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SELECTIVE DIRECT BORYLATION AND LATE-STAGE FUNCTIONALIZATION OF 1,2-AZABORINES

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ABSTRACT: Described herein is the development of a method to directly borylate the C5-position of monocyclic 1,2-azaborines without the use of a metal catalyst, kinetic resolution or directing group. This method tolerates different substitution on the boron as well as at the C3-position of the azaborine. A new BN-isostere of the drug molecule, felbinac, was synthesized to demonstrate the application of this method.

For Kay

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List of Abbreviations

Ala: alanine

Ar: aryl

atm: atmosphere(s)

AUC_{po}: area under the curve after oral treatment

azaborine: monocyclic 1,2-azaborine

$B_2(pin)_2$: bis(pinacolato)diboron

BBr_3: boron tribromide

BDE: homolytic bond dissociation energy

Boc: *t*-butoxycarbonyl

Br: broad

Bu: butyl

C_{max}: concentration

CDK2: cyclin-dependent kinase 2

cod: 1,5-cyclooctadiene

conv: conversion

Cy: cyclohexyl

D: debye

D3: dopamine receptor

d: doublet

DART: direct analysis in real time

DCM: dichloromethane

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

dd: doublet of doublets

ddt: doublet of doublet of triplets

DMSO: dimethylsulfoxide

Dq: doublet of quartets

DTBP: 2,6-ditertbutylpyridine

dtbpy: 4,4'-di-tert-butyl-2,2'-bipyridyl

E: electrophile

EAS: electrophilic aromatic substitution

eq: equation

equiv: equivalent(s)

Et: ethyl

EbDH: ethylbenzene dehydrogenase

GC-MS: gas chromatography-mass spectrometry

Gln: glutamine

h: hour(s)

HRMS: high resolution mass Spectrometry

i: iso

IC_{50}: half maximal inhibitory concentration

Ile: isoleucine

IR: infrared spectroscopy

L: ligand

LAH: lithium aluminum hydride

LDA: lithium diisopropyl amide

Leu: leucine

$LiBHEt_3$: lithium triethylborohydride

M: molar

m: multiplet

Me: methyl

Mes: mesityl

Met: methionine

min: minute(s)

MTBE: methyl tert-butyl ether

NMO: N-methylmorpholine N-oxide

NMR: nuclear magnetic resonance spectroscopy

NSAID: nonsteroidal anti-inflammatory drug

Nu: nucleophile

OAc: Acetoxy

OTf: trifluoromethanesulfonate

o-Tol: *ortho*-tolyl

Ph: phenyl

pin: pinacol

PPAR: peroxisome proliferator-activated receptor

PPh_3: triphenylphosphine

Pr: propyl

q: quartet

RT: room temperature

s: singlet

solv: solvent

t: tert

t: triplet

$t_{1/2}$: half-life

t_{max}: time

TBAF: tetrabutylammonium fluoride

TBS: *t*-butyldimethylsilyl

TCE: tetrachloroethane

td: triplet of doublets

Temp: temperature

THF: tetrahydrofuran

tol: toluene

CHAPTER 1

Selective Direct Borylation and Late-Stage Functionalization of 1,2-Azaborines

1.1 Introduction to BN/CC Isosterism and Azaborines

The concept of isosteres, or isosteric compounds, was first proposed by Irving Langmuir in 1919.[1] Langmuir developed this concept when comparing the physical properties of carbon dioxide and nitrous oxide (Table 1.1). The similarities in their physical properties led Langmuir to further investigate this phenomenon. He subsequently found many other molecules that had properties closely related to one another and was able to solidify his definition. He described isosteres as having the same number and arrangement of electrons.[1] This definition is not limited to describing chemical compounds, but also radicals or atoms which hold a pair of electrons in common. Langmuir's introduction to isosterism opened many new doors and changed the way the chemical field evolved.

Table 1.1: Comparison of Carbon Dioxide and Nitrous Oxide's Physical Properties

Property	N_2O	CO_2
Critical pressure (atm.)	75	77
Critical temp (°C)	35.4	31.9
Viscosity at 20°C	148×10^{-6}	148×10^{-6}
Heat conductivity at 100°C	0.0506	0.0506
Density of liquid at –20°C	0.996	1.031
Density of liquid at +10°C	0.856	0.858
Refractive index of liquid, D line, 16°C	1.193	1.19
Dielectric constant of liquid at 0°C	1.598	1.582
Magnetic susceptibility of gas at 40 atm., 16°C	0.12×10^{-6}	0.12×10^{-6}
Solubility in water at 0°C	1.305	1.78
Solubility in alcohol at 15°C	3.25	3.13

[1] Langmuir, I. *J. Am. Chem. Soc.* **1919**, *41*, 1543–1559.

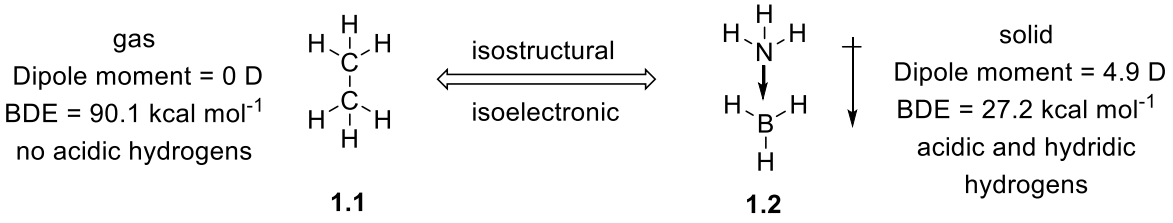
Throughout the years, the concept of an isostere has been expanded upon and modified. Through the pioneering work of Grimm,[2] Penny and Southerland,[3] the term has been adapted to include two additional properties, isoelectronic and isostructural. Though the definition is ambiguous, isoelectronic compounds are most widely defined as two or more species having the same total number of both atoms and electrons.[4] Isostructural compounds are defined as two or more species being similar in atomic connectivity and structure. These two terms are closely associated and both are required for chemical compounds to be considered isosteres.

Of the various isosteres known, one that has gained much interest over the years has been the isosterism between a carbon-carbon unit and a boron-nitrogen unit, typically referred to as BN/CC isosterism.[5] BN/CC isosterism is particularly of interest because it allows for molecules to be built which are isoelectronic to their carbon analogues but display different electronic properties induced by the boron and nitrogen. The simplest comparison can be made using the hydrocarbon ethane (**1.1**) and its isostere, the ammonia-borane adduct (**1.2**). The first noticeable difference between these two compounds stems from their physical state of matter. At room temperature, ethane is a volatile gas while ammonia-borane is a solid due to its strong intramolecular interactions.[6] In addition to the difference in physical properties, these compounds also differ in their electronic properties. **1.1** is a nonpolar molecule with a bond dissociation energy (BDE) of

[2] (a) Grimm, H. G. Z. *Elektrochem*. **1925**, *31*, 474–480.; (b) Grimm, H. G. *Naturwissenschaften* **1929**, *17*, 557–564. (c) Grimm, H. G.; Gunther, M.; Tittus, H. Z. *Physik. Chem.* **1931**, *14*, 169.
[3] Penney, W. G.; Sutherland, G. B. B. M. *Force Constants of Triatomic Systems.* **1936**, 654–678.
[4] Rayner-Canham, G. *Found. Chem.* **2009**, *11* (2), 123–129.
[5] For a brief overview, see: (a) Liu, Z.; Marder, T. B.; *Angew. Chem. Int. Ed.* **2008**, *47*, 242–244. (b) *Angew. Chem*. **2008**, *120*, 248–250. (c) Bosdet, M. J. D.; Piers W. E. *Can J. Chem*. **2009**, *87*, 8–29. (d) Campbell, P. G.; Marwitz, A. J. V.; Liu, S.-Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 6074–6092. (e) Giustra, Z. X.; Liu, S.-Y.; *J. Am. Chem. Soc*. **2018**, *140*, 1184–1194.
[6] Liu, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 242–244.

90.1[7] kcal mol^{-1} and contains only slightly acidic hydrogens due to the similarities in the electronegativity values of carbon and hydrogen. Conversely, **1.2** is a polar molecule that has a bond dissociation energy of 27.2 kcal mol^{-1} and a dipole moment of 4.9 debye.[8,9] In addition, the hydrogens in the adduct are different in reactivity. Due to the differences in electronegativities, the hydrogens connected to the nitrogen are acidic while the hydrogens on the boron are hydridic (Figure 1.1).[10] The differences in chemical nature of these hydrogens allow for the adduct to be much more reactive than its isosteric counterpart, ethane, thus accentuating the importance of BN/CC isosterism.

Figure 1.1: Comparison of Properties between Isosteric Compounds Ethane and Ammonia-Borane Adduct[6,7,8,9]

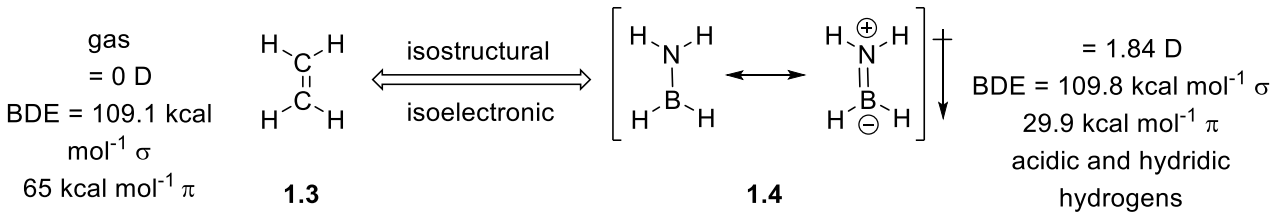


The clearest example of BN/CC isosterism arises from the isosterism between ethene (**1.3**) and aminoborane (**1.4**). Similar to its saturated counterpart **1.1**, **1.3** is volatile gas under standard pressure and temperature with no effective dipole moment and unreactive C-H bonds. It has a bond dissociation energy of 174.1 kcal mol^{-1}, with the σ bond contributing 109.1 kcal mol^{-1} and the π bond contributing the remaining 65 kcal mol^{-1}.[7,11] Conversely, ethene's BN analogue, **1.4**, is

[7] Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res*. **2003**, *36,* 255–263.
[8] Grant, D. J.; Dixon, D. A. *J. Phys. Chem*. **2006**, *110*, 12955–12962.
[9] You, A.; Be, M. A. Y.; In, I. *J. Chem. Phys.* **1958**, *29*, 3–5.
[10] Qiu, B.; Wang, W.; Yang, X. *Front. Chem.* **2019**, *7*, 627–637.
[11] Alkorta, I.; Elguero, J. *Struct. Chem.* **1998**, *9*, 59 – 63.

unstable at room temperature due to its reactive nature and propensity to polymerize. Despite this, Matsumura and coworkers[12] were able to characterize the compound by microwave spectroscopy and found the molecule to have C_{2v} symmetry with a planar structure similar to that of ethene, along with a dipole moment equal to 1.84 debye. Unlike **1.3**, **1.4** has a much lower π bond contribution of only 29.9 kcal mol^{-1} leading to an overall bond dissociation energy of 139.7 kcal mol^{-1} (Figure 1.2) .[8]

Figure 1.2: Comparison of Properties between Isosteric Compounds Ethene and Aminoborane[7,8,9,11]

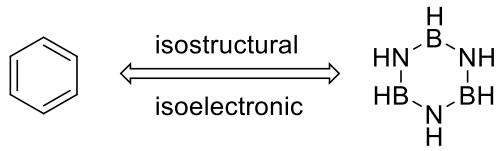


1.1.1 Initial Discovery of Monocyclic Azaborines

Expanding the sp^2-type BN/CC isosterism to more complex molecules allows for the modification of the electronic properties of many different arenes and aromatic compounds. The first successful example of BN/CC isosterism in an aromatic compound was completed by Alfred Stock in 1926.[13] Stock reported borazine (**1.6**), the first isostere of benzene (**1.5**) in which all of the CC double bonds were replaced with a BN unit. Stock's initial report and characterization of **1.6** sparked what would become decades long of interest and research into BN isosteres of aromatic compounds (Figure 1.3).

[12] Sugie, M.; Takeo, H.; Matsumura, C. *Chem. Phys. Lett*. **1979**, *64*, 573–575.
[13] Stock, A.; Pohland, E. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 2210–2215.

Figure 1.3: BN/CC Isosterism between Benzene and Borazine

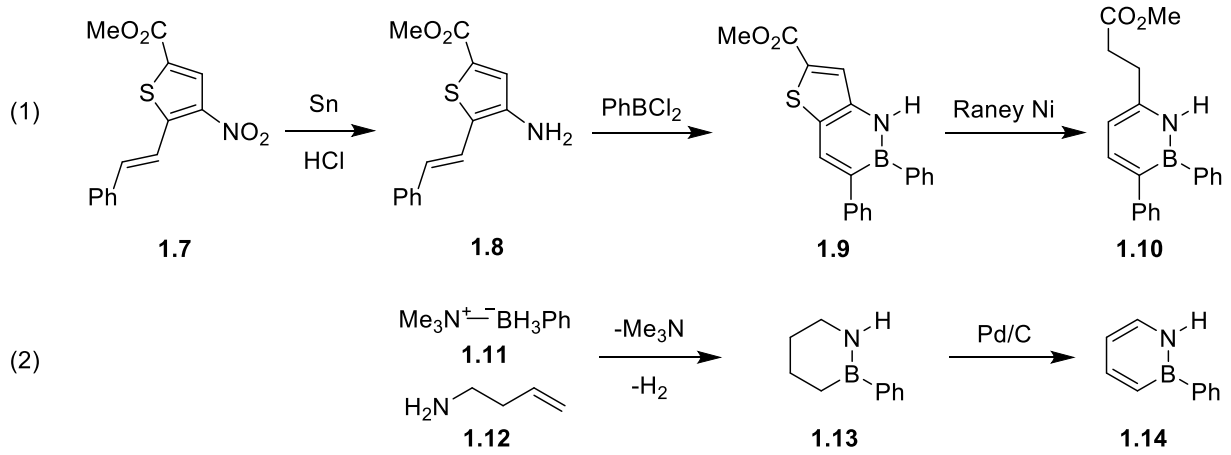


1.5 **1.6**

Since Stock's development of benzene's inorganic counterpart, Michael J. S. Dewar greatly expanded the field of BN/CC isosterism and introduced different examples of arene isosteres containing only one BN unit.[14,15] Of particular interest are 1,2-azaborine derivatives, which are benzene isosteres where a BN unit replaces one CC double bond. These 1,2-azaborines served as a hybrid structure between the fully organic benzene and its inorganic counterpart, borazine. The first example of a monocyclic substituted 1,2-azaborine was synthesized by Dewar in 1962 through the desulfurization of compound **1.9** to afford **1.10** (Scheme 1.1, eq 1).[16] Within the next year, White and coworkers synthesized their own 1,2-azaborine (**1.14**) which had no substitution on the carbon backbone of the molecule (Scheme 1.1, eq 2).[17]

[14] a) Dewar, M. J. S.; Kubba, V. P.; Pettit, R. *J. Chem. Soc.* **1958**, 3073–3076. b) Dewar, M. J. S.; Dietz, R. *J. Chem. Soc.* **1959**, 2728–2730. c) Dewar, M. J. S.; Gleicher, G. J.; Robinson, B. P. *J. Am. Chem. Soc.* **1964**, *86*, 5698–5699.
[15] Fritsch, A. J. *Chem. Heterocycl. Compd.* **1977**, *30*, 381–440.
[16] Dewar, M. J. S.; Marr, P. A. *J. Am. Chem. Soc.* **1962**, *84*, 3782.
[17] White, D. G. *J. Am. Chem. Soc.* **1963**, *85*, 3634–3636.

Scheme 1.1: Dewar and White's Syntheses of 1,2-Azaborine Derivatives[16,17]



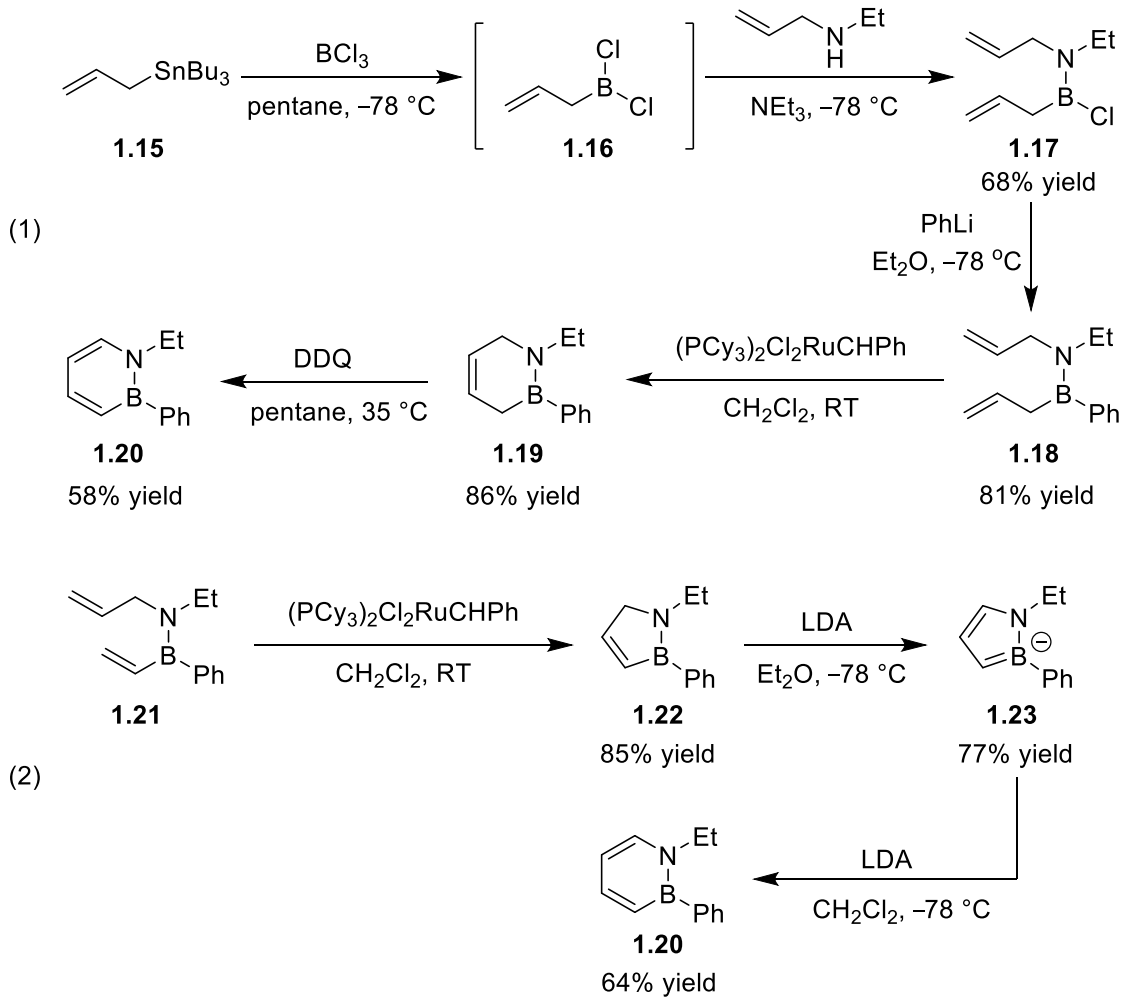
1.1.2 New Developments of Azaborines

After the initial syntheses of 1,2-azaborines by Dewar and White, the progress in this field slowed until a breakthrough by Ashe in 2000 revitalized the field. Ashe reported two straightforward syntheses of *N*-Et, *B*-Ph 1,2-azaborine (**1.20**) that featured a robust ring closing metathesis[18] and a ring expansion method.[19] In the first synthesis, allylboron dichloride (**1.16**) is generated *in situ* through the reaction of allyltributyltin (**1.15**) with boron trichloride. Subsequent reaction with ethyl allylamine in the presence of triethylamine resulted in the formation of adduct **1.17** in 68% yield. This species then cleanly reacted with phenyllithium to give product **1.18** in 81% yield and a subsequent ring closing metathesis with Grubbs first generation catalyst[20] gave the six membered heterocycle **1.19** in 86% yield. The final aromatized product **1.20** was obtained in modest yield through a DDQ oxidation (Scheme 1.2, eq 1). The second synthesis proceeded through a ring closing metathesis of diallyl-adduct **1.21** to afford the five membered heterocycle

[18] Ashe, A. J., III; Fang, X. D. *Org. Lett*. **2000**, *2*, 2089–2091.
[19] Ashe, A. J.; Fang, X.; Fang, X.; Kampf, J. *Organometallics*, **2001**, *20*, 5413–5418.
[20] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041.

1.22 in 85% yield. Deprotonation with LDA resulted in the lithium azaborolide **1.23** in 77% yield and a final ring expansion gave the desired product **1.20** in 64% yield (Scheme 1.2, eq 2).

Scheme 1.2: Ashe's Syntheses of *N*-Et, *B*-Ph 1,2-Azaborine

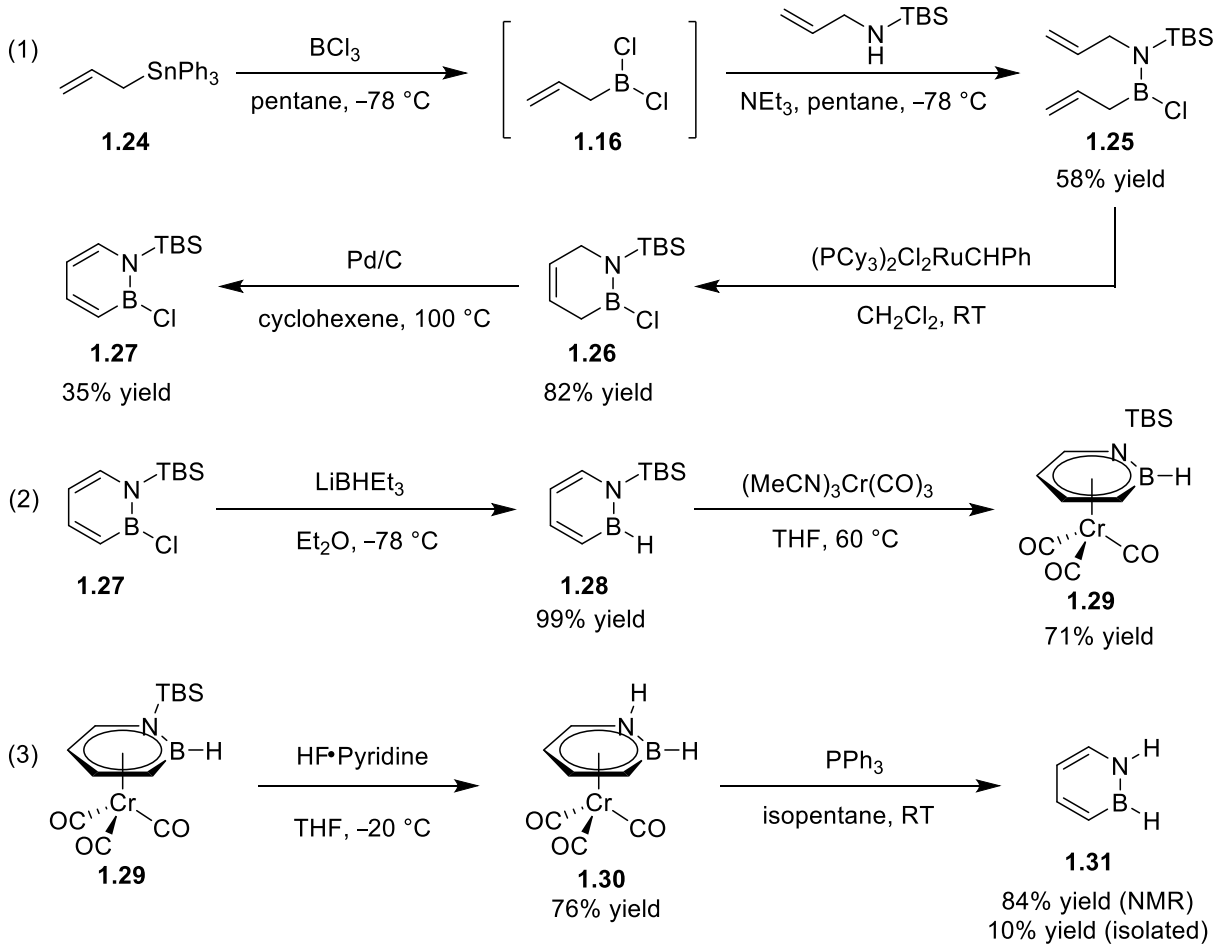


After Ashe's breakthrough, the chemical field of azaborines exploded with newfound interest. Of particular note, Liu *et al*. reported the synthesis of *N*-TBS, *B*-Cl 1,2-azaborine (**1.27**) through a modified version of Ashe's procedure, and the successful synthesis of the long-sought

parent 1,2-dihydro-1,2-azaborine (**1.31**) in 2009.[21] Liu's new synthetic method still had a key ring closing metathesis step but afforded the desired azaborine in one less step (Scheme 1.3, eq 1). Besides this, the *N*-TBS, *B*-Cl 1,2-azaborine introduced an easily removable protecting group on the nitrogen and a labile *B*-Cl bond which is easily modified. These two features were key in finally achieving the synthesis of the parent azaborine. From **1.27**, the *B*-H bond was installed through a nucleophilic substitution with $LiBHEt_3$. It was found that complexation to "$Cr(CO)_3$" was necessary in order for desilylation to occur. The resulting adduct **1.29** was obtained in 71% yield. The *N*-protecting group was then removed and a final decomplexation with PPh_3 afforded the parent 1,2-dihydro-1,2-azaborine **1.31** in 10% isolated yield (Scheme 1.3, eq 2&3).

[21] Marwitz, A. J. V.; Matus, M. H.; Zakharov, L. N.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 973–977.

Scheme 1.3: Liu's Syntheses of *N*-TBS, *B*-Cl 1,2-azaborine and the Parent 1,2-dihydro-1,2-azaborine[21]

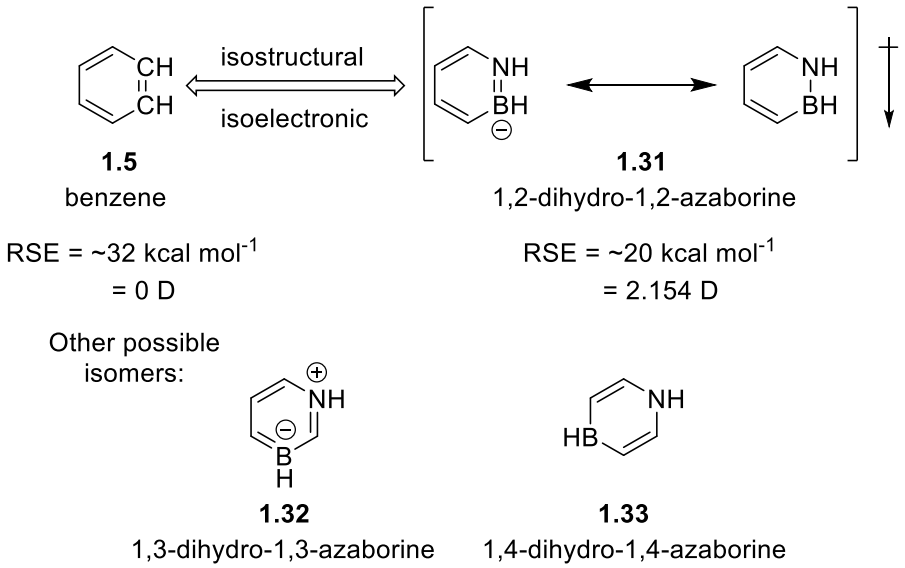


Consistent with BN/CC isosterism, 1,2-dihydro-1,2-azaborine (**1.31**) is similar in structure to benzene but displays distinct electronic properties. Like its carbonaceous analogue, **1.31** displays aromaticity with a calculated resonance stabilization energy of 19.6 kcal mol^{-1}.[22] Unlike its analogue, it has both a hydridic and acidic proton which is capable of hydrogen bonding,[23] as

[22] Campbell, P. G.; Abbey, E. R.; Neiner, D.; Grant, D. J.; Dixon, D. A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 18048–18050.
[23] Lee, H.; Fischer, M.; Shoichet, B. K.; Liu, S.-Y. *J. Am. Chem. Soc.* **2016**, *138*, 12021–12024.

well as a dipole moment of 2.154 debye.[24] Besides the 1,2-azaborine isostere, there also exists the 1,3-dihydro-1,3-azaborine (**1.32**) and 1,4-dihydro-1,4-azaborine (**1.33**) isosteres, that also display distinct electronic properties but are not as prevalent as 1,2-azaborines, which are the focus of this work (Figure 1.4).

Figure 1.4: BN/CC Isosterism between Benzene and Azaborine Isomers



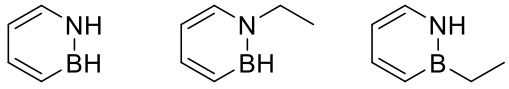
1.1.3 Importance of Azaborines in Medicinal Chemistry

The different electronic properties displayed in azaborines can be utilized to expand upon the properties of current drug molecules. The BN analogues of arenes are of interest due to the abundance of arenes and aromatic compounds in biomedical research. The first example of azaborines interacting with a biological system was shown by Liu, Matthews, and coworkers in 2009 where they demonstrated that azaborines had the capability to bind inside a nonpolar cavity

[24] Chrostoswka, A.; Xu, S.; Lamm, A. N.; Mazière, A.; Weber, C. D.; Dargelos, A.; Baylère, P.; Graciaa, A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 10279–10285.

of a mutated T4 lysozyme via a Leu99Ala mutation.[25] The BN analogues of benzene and ethylbenzene were synthesized and their binding abilities compared to the carbon analogues. It was found that the azaborines have the capability to bind in the aryl recognition pockets and that both the parent 1,2-azaborine (**1.31**) and *N*-ethyl-1,2-azaborine (**1.34**) bind with almost 100% occupancy (40% more occupancy than ethylbenzene). Additionally, similar work by Liu showed that **1.31** and *B*-ethyl-1,2-azaborine (**1.35**) can bind in a double mutated polar pocket of T4 lysozyme developed by Matthews in which methionine 102 is mutated to a glutamine residue (Figure 1.5).[23] It was found through high-resolution protein X-ray crystallography that the NH group of **1.31** and **1.35** engages in hydrogen bonding with the oxygen of the mutated glutamine residue in the pocket. The observed distances between the NH group of the azaborines and the Gln102 carbonyl oxygen is 3.1 Å and 3.2 Å for **1.31** and **1.35,** respectively. The binding energies of hydrogen bonding between the Gln102 carbonyl oxygen and NH of the parent azaborine, as well as the NH of **1.35** were estimated to be −0.94 and −0.64 kcal/mol, respectively. Finally, further studies into the strength of the hydrogen bond showed that bulkier groups on the boron of the azaborine lead to weaker hydrogen bonds.[26]

Figure 1.5: Azaborines Shown to be Capable of Binding in Aryl Recognition Pockets of Enzymes[23,25]



1.31 **1.34** **1.35**

[25] Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 6817 –6819.
[26] Liu, Y.; Liu, S.-Y. *Org. Biomol. Chem.* **2019**, *17*, 7002–7006.

After these initial discoveries, Liu, Heider, Szaleniec, and coworkers expanded upon this work by showing that the same azaborine isosteres of ethylbenzene could also act as enzyme inhibitors.[27] Ethylbenzene dehydrogenase (EbDH) is a molybdenum enzyme, which belongs to the DMSO reductase family that catalyzes the stereoselective hydroxylation of ethylbenzene to (*S*)-1-phenylethanol in anaerobic conditions.[28] While ethylbenzene acts as a substrate for EbDH, Liu *et al*. was able to show that both *B*- and *N*-ethyl BN isosteres of ethylbenzene are strong inhibitors of ethylbenzene dehydrogenase. It was found that **1.35** had an IC_{50} value of 100 μM, whereas **1.34** was more potent with an IC_{50} value of only 2.8 μM. Upon further investigation, it was seen that **1.35** had a slightly different orientation in the binding site, accounting for the decreased inhibitory effect. These differences between ethylbenzene and its BN isosteres prove that not only can BN/CC isosterism be applied in a biological context but it can also lead to unique behavior.

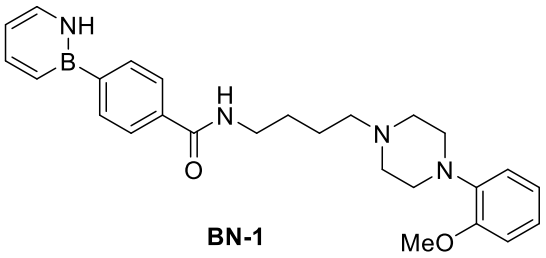
After showing azaborines could be applied in a biological setting, Liu and coworkers were also able to synthesize the first examples of biologically active monocyclic 1,2-azaborines.[29] They synthesized the BN analogues of 3 known biologically active biphenyl carboxamides (biaryls are considered to be privileged structures[30]) and evaluated their bioactivities in comparison to their carbonaceous isosteres. Compounds **BN-1**, **BN-2**, and **BN-3** have been synthesized as the isosteres of dopamine receptor D3, PPAR γ and δ, and CDK2 inhibitors, respectively, and were shown to be air and water stable. D3 is a dopamine receptor protein in humans and is a target for drugs that

[27] Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 2599 –2601.
[28] Johnson, H. A.; Pelletier, D. A.; Spormann, A. M. *J. Bacteriol.* **2001**, *183*, 4536–4542.
[29] Zhao, P.; Nettleton, D. O.; Karki, R. G.; Zécri, F. J.; Liu, S.-Y. *ChemMedChem* **2017**, *12*, 358–361.
[30] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

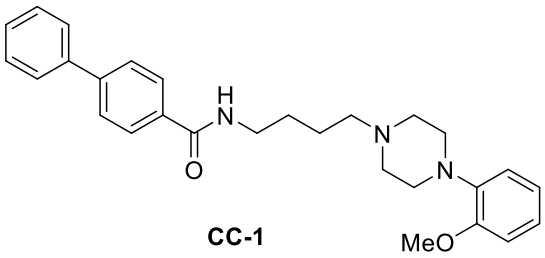
treat neurological disorders including: Parkinson's disease, schizophrenia and drug abuse.[31,32] It's analogue, **BN-1**, was shown to have an increased solubility, as well as an IC_{50} value of 3 nM. PPAR γ and δ are nuclear receptor proteins that regulate the expression of genes.[33] These proteins have been involved in the development of numerous diseases including diabetes, obesity, atherosclerosis and cancer and their antagonists have been used to treat hyperlipidemia and hyperglycemia.[34,35] Its corresponding **BN-2** compound again had an increased solubility and IC_{50} values of 2 nM and 1 nM for PPAR γ and δ, respectively. Finally, CDK2 is a serine/threonine protein kinase that was reported as a potent nanomolar antiproliferate agent.[36] CDK2 antagonists have been found to be useful for chemotherapy and chemoprevention against certain cancers.[37] Again, its BN isostere, BN-3, showed an improved solubility, as well as an improved IC_{50} value of 87 nM (Figure 1.6).

[31] Joyce, J. N.; Millan, M. J. *Current Opinion in Pharmacology*. **2007**, *7*, 100–105.
[32] Maramai *et al*. *Front. Neurosci.* **2016**, *10*, 1–16.
[33] Michalik, L.; Wahli, W. *Pharmacol. Rev.* **2006**, *58*, 726–741.
[34] (a) Berger, J.; Moller, D. E. *Annu. Rev. Med*. **2002**, *53,* 409–435. (b) Feige, J. N.; Gelman, L.; Michalik, L.; Desvergne, B.; Wahli, W. *Prog. Lipid Res.* **2006**, *45,* 120–159.
[35] (a) Lehrke, M.; Lazar, M. A.; *Cell*. **2006**, *123*, 993–999. (b) Kim, J. H.; Song, J.; Park, K. W.; *Arch. Pharmacal. Research* **2006**, *38,* 302–212.
[36] Pevarello, P.; Warpehoski, M. A. *J. Med.Chem.* **2004**, *47*, 3367–3380.
[37] Peng, C.; Zeng, W.; Su, J.; Kuang, Y.; He, Y.; Zhao, S.; Zhang, J.; Ma, W.; Bode, A. M.; Dong, Z.; Chen, X. *Oncogene* **2016**, *35*, 1170–1179.

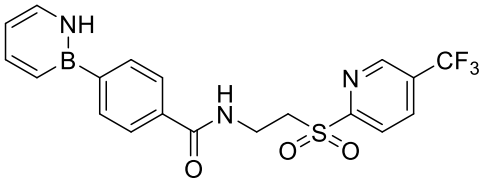
Figure 1.6: Comparison of Biologically Active Molecules to Their BN-Analogues[29]



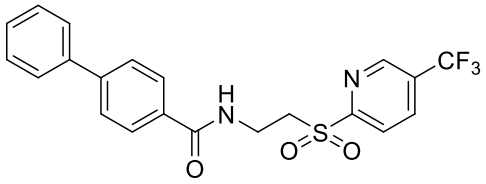
BN-1
Sol. = 0.046 mM
IC_{50} = 3 nM



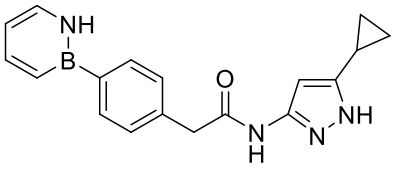
CC-1
Sol. = <0.005 mM
IC_{50} = 1 nM



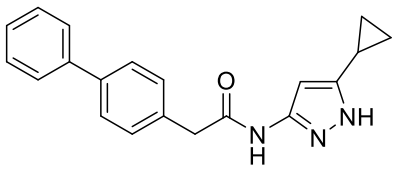
BN-2
Sol. = <0.004 mM
PPAR IC_{50} = 2 nM
PPAR δ IC_{50} = 1 nM



CC-2
Sol. = <0.004 mM
PPAR γ IC_{50} = 1 nM
PPAR δ IC_{50} = 2 nM



BN-3
Sol. = 0.013 mM
IC_{50} = 87 nM

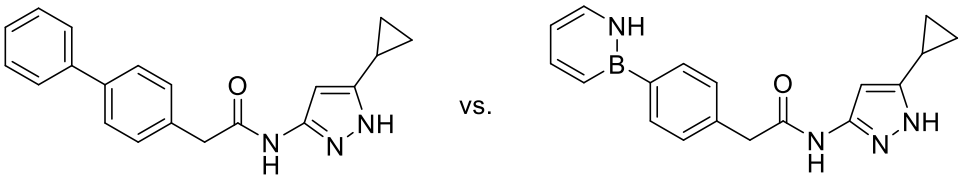


CC-3
Sol. = <0.004 mM
IC_{50} = 320 nM

The improved solubility of each BN antagonist can be attributed to the introduction of the polar B-N bond unit, rendering the molecule to be less hydrophobic. As a result of the improved solubility, **BN-3** showed improved in vivo pharmokinetic behavior, including a doubled AUC_{po}, higher bioavailability, and a longer terminal half-life (Figure 1.7). The observed improved biological activity is likely a result of the NH group acting as a hydrogen bond donor. It can be seen through docking models that the amine of the azaborine can hydrogen bond with the carbonyl

backbone of Ile10 in the ATP binding pocket. These results with the BN analogues highlight the importance of incorporating azaborines into bioactive molecules and emphasize the need to be able to functionalize these azaborines at their different positions for the synthesis of compound libraries.

Figure 1.7: Bioactivities of the CDK2 Inhibitor versus the BN-Analogue



	CC-3	BN-3
AUCpo:	283 nM• h	613 nM• h
Bioavailability:	22.5 %	29.3 %
$t_{1/2}$:	10.5 h	11.6 h
t_{max}:	0.5 h	1.5 h
C_{max}:	692 nM	746 nM

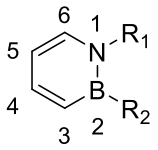
1.1.4 Present Gap in Azaborine Functionalization

To expand the chemical space of azaborines, there must be methods to functionalize each position of the azaborine. This would allow for new biomimetics and BN drug molecules to be developed and used in a medical setting. Fortunately, due to the lack of symmetry present in azaborines, each position is chemically independent.[38] The distinction in chemical character allows for specific positions to be selectively functionalized. There have been methods developed to

[38] Baggett, A. W.; Vasiliu, M.; Li, B.; Dixon, D. A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2015**, *137*, 5536–5541.

selectively incorporate different functional groups on the boron and nitrogen atoms.[39,40] Similarly, procedures have been developed to selectively functionalize both C3 and C6 of the carbon backbone (*vide infra)*. However, there are very few methods developed to directly functionalize the C5 carbon.[41,42,43] To date, there has yet to be a method developed to directly and selectively borylate the C5 carbon.

Figure 1.8: Position Labelling for the Monocyclic 1,2-Azaborines



The ability to directly functionalize the position para to the boron would also expand the chemical space of biphenyl motifs. So far, these structures have only been accessed through the aryl substitution on the boron (*vide supra*). However, installation of different functional groups at the C5-position would allow for an unsubstituted phenyl ring to be present on the boron in the biphenyl and thereby further expand the structural diversity. This work describes a new methodology directed at addressing the gap in the current functionalization of azaborines.

[39] Marwitz, A. J. V.; Abbey, E. R.; Jenkins, J. T.; Zakharov, L. N.; Liu, S.-Y. *Org. Lett.* **2007**, *9*, 4905−4908.
[40] Lamm, A. N,; Garner, E. B,; Dixon, D. A.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 8157−8160.
[41] Zhang, Y.; Sun, F.; Dan, W.; Fang, X. *J. Org. Chem.* **2017**, *82*, 12877−12887.
[42] Zhang, Y.; Dan, W.; Fang, X. *Organometallics,* **2017**, *36*, 1677−1680.
[43] Pan, J.; Kampf, J. W.; Ashe, A. J. *Org. Lett*. **2007**, *9*, 679−681.

1.2 Direct Borylation of Arenes

1.2.1 Background

C-H borylation has been developed and explored over the years as an important transformation in organic chemistry.[44] The introduction of the versatile C-B bond generates new organoboron reagents[45] that can be used as a linchpin to construct pharmaceuticals and natural products.[46] Among the methods known to incorporate these bonds, transition metal-catalyzed reactions are well established.[47] Similarly, alternative procedures have been developed that do not require the use of a metal to integrate the C-B bond.[48] These reactions can be achieved simply through the use of boron halides as the borylation reagent. Despite the difference in conditions, both of these methods have the capability to introduce a versatile functional group (i.e. Bpin), which can be transformed into various groups including: halogens,[49] perfluoroalkyl,[50] OH,[51] OR,[52]

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[44] For representative reviews, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864−873. (c) Piers, W. E.; Bourke, S. C.; Conroy, K. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 5016−5036. (d) De Vries, T. S.; Prokofjevs, A.; Vedejs, E. *Chem. Rev.* **2012**, *112*, 4246−4282.

[45] (a) Pelter, A.; Smith, K.; Brown, H. C. Borane Reagents; Academic: London, **1988**. (b) Hall, D. Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, 2nd ed.; WileyVCH: Weinheim, **2011**. (c) Suzuki, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6722−6737. (d) Oeschger et al., *Science,* **2020**, *368*, 736–741.

[46] (a) Matteson, D. S. Stereodirected Synthesis with Organoboranes; Springer: Berlin, **1995**. (b) Suzuki, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6722−6737.

[47] (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110,* 890−931. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40,* 1992−2002. (c) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138,* 2−24.

[48] Ingleson, M. J. *Synlett* **2012**, 1411−1415.

[49] (a) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **2013**, *135*, 2552−2559. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc*. **2007**, *129*, 15434−15435. (c) Partridge, B. M.; Hartwig, J. F. *Org. Lett.* **2013**, *15*, 140−143.

[50] (a) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2012**, *51*, 536−539. (b) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230−1233.

[51] (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc*. **1980**, *102*, 7591−7593. (b) Kabalka, G. W.; Shoup, T. M.; Goudagaon, N. M. *Tetrahedron Lett*. **1989**, *30*, 1483−1486. (c) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett*. **2010**, *12*, 1964−1967. (d) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jorgensen, K. A.; Xiao, W.-J. *Angew. Chem. Int. Ed*. **2012**, *51*, 784-788. (e) Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2013**, *52*, 2092−2095.

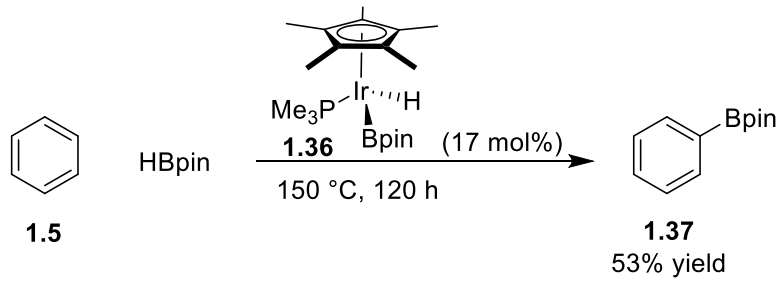
[52] Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc*. **2010**, *132*, 1202−1203.

NH_2,[53] $B(OH)_2$,[54] and BF_3K.[55] This ability to introduce a wide range of new functional groups allows for a new way to diversify arenes through C-H borylation.

1.2.2 Iridium Catalyzed C-H Borylation

Transition metal catalyzed C-H borylation of arenes was first fully developed in 1995 by Hartwig and coworkers, used $(CO)_5MnBcat$, $(CO)_5ReBcat$, and $CpFe(CO)_2Bcat$ as catalysts to borylate both benzene and toluene.[56] Since this initial discovery, many transition metals have been utilized as the catalyst, [47a] but of these iridium complexes have been shown to be particularly successful. Smith and Iverson were the first to report the C-H borylation of an unreactive arene using an Cp*Ir $(PMe_3)(H)(Bpin)$ (**1.36**) (Scheme 1.4).[57]

Scheme 1.4: Smith and Iverson's Borylation Reaction of Benzene using an Iridium Catalyst



This reaction provided a novel way to directly borylate unreactive arenes however, it was limited by a turnover number of only 3. Despite the lack of efficiency in the reaction, Hartwig and coworkers[58] expanded upon their previous work and developed efficient and milder conditions to

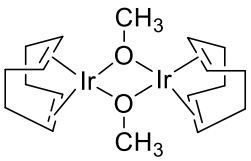
[53] (a) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett*. **2007**, *9*, 761−764. (b) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc*. **2012**, *134*, 16449−16451.
[54] (a) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics*, **1984**, *3*, 1284−1288. (b) Sun, J.; Perfetti, M. T.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3571−3575
[55] Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett*. **2007**, *9*, 757−760.
[56] Waltz, K. M.; He, X.; Muhoro, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11357.
[57] Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc*. **1999**, *121*, 7696−7697.
[58] (a) Waltz, K. M.; Muhoro, C. N.; Hartwig, J. F. *Organometallics* **1999**, *18*, 3383–3393. (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651. (c) Ishiyama, T.; Takagi, J.; Hartwig, J. F.;

borylate different arenes and heteroarenes. In collaboration with Ishiyama and Miyaura, they catalyzed the borylation of arenes and heteroarenes at room temperature using 1/2[Ir(OMe)(COD)]$_2$ (**1.38**) complexes with air stable 2,2'-bipyridines and stoichiometric amount of inexpensive pinacolborane (Table 1.2).[59]

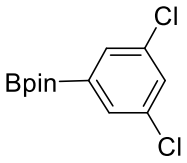
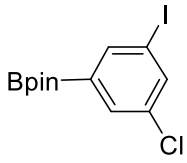
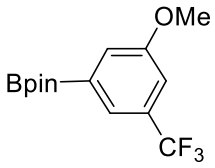
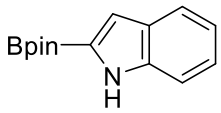
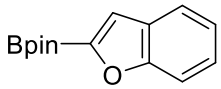
Miyaura, N. *Angew. Chem. Int. Ed*. **2002**, *41*, 3056−3058. (d) Di, V.; V, H. U.; Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391.

[59] Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N.; Haven, N. *Chem. Commun*. **2003**, 2924–2925.

Table 1.2: C-H Borylation of Arenes and Heteroarenes using an Ir(I) Complex[59]



H–Bpin (1.1 equiv) + Aryl–H (1 equiv) → **1.38** (1.5 mol%), dtbpy (3 mol%), hexane, RT → Aryl–Bpin + H_2

Entry	Product	Time (h)	Yield (%)
1		8	86
2		8	67
3		24	73
4		0.5	99
5		1	90

It was found that for these reactions with arenes, sterics seemed to govern the selectivity. Conversely, further investigation revealed that using the same conditions on heteroarenes lead to selectivity largely controlled by electronic effects.[59,60,61] The reaction occurs at the C-H bond alpha

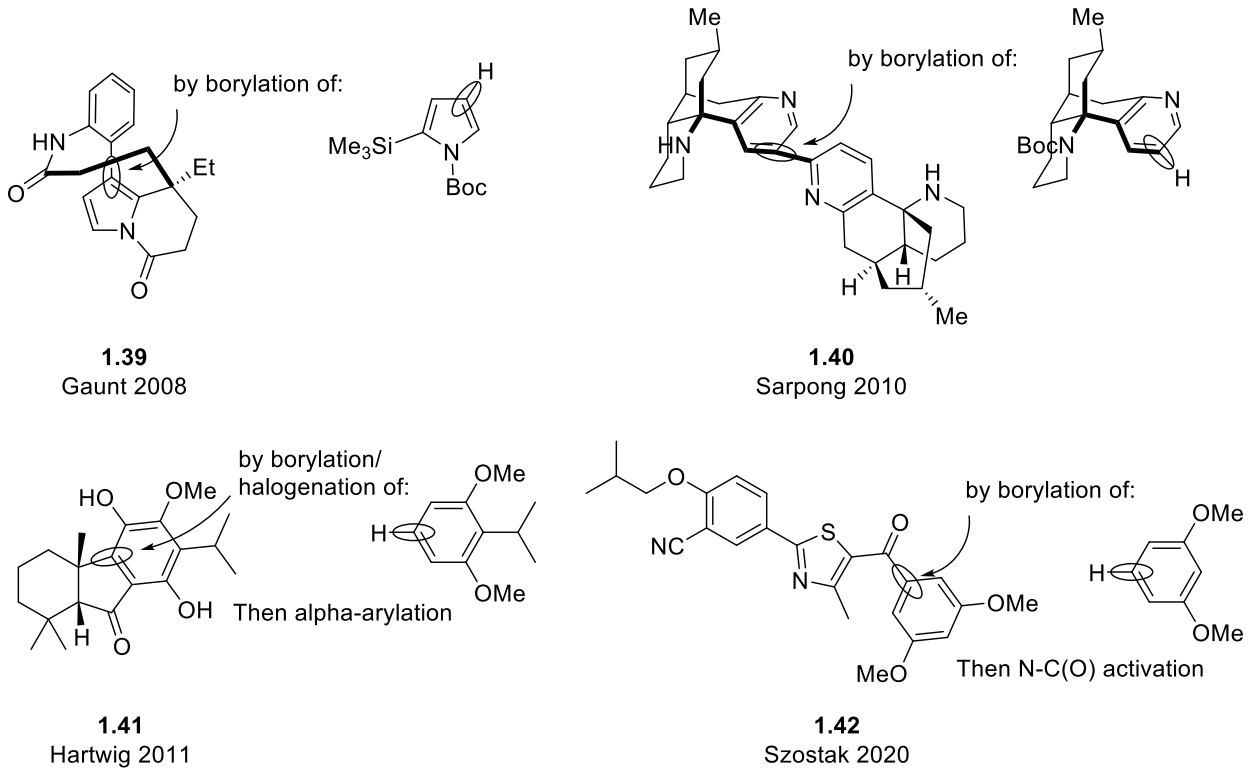
[60] Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal*. **2003**, *345*, 1103–1106.
[61] Vanchura, I. I. B. A.; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, J. R. E.; Singleton, D. A.; Smith, M. R. *Chem. Commun.* **2010**, *46*, 7724–7726.

to the heteroatom and even in the case of benzo-fused heterocycles, no reaction occurs at the benzene ring. However, it is possible to modify this selectivity using steric effects. If a nitrogen-containing heteroarene contains a large substituent on the nitrogen atom, the reaction takes place beta to the nitrogen.[50,62]

The development of iridium catalyzed C-H borylation not only leads to a higher functional group tolerance with more mild conditions,[58d] but it could also be utilized as a key step in the synthesis of active pharmaceutical ingredients and natural products (Scheme 1.5). In 2008, Gaunt and coworkers reported the synthesis of the pyrrole alkaloid rhazinicine (**1.39**) through the iridium catalyzed C-H borylation of an *N*-Boc-pyrrole derivative.[62] Similarly, Sarpong and coworkers were able to take advantage of the selectivity of pyridine borylation to synthesize the alkaloid (+)-complanadine A (**1.40**).[63] The installation of the beta boryl group allowed for a Suzuki-Miyaura cross coupling to form the biaryl bond in their final steps. Additionally, Hartwig and coworkers were able to synthesize the natural product (-)-taiwaniaquinol B (**1.41**) through an α-arylation of the aryl halide that was generated after C-H borylation and subsequent halogenation.[64] More recently, Szostak and coworkers were able to prepare febuxostat (**1.42**) via the iridium catalyzed C-H boylation of 1,3-dimethoxybenzene followed by subsequent decarbonylative amide N-C(O) activation.[65]

[62] Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004–3007.
[63] Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc*. **2010**, *132*, 5926–5927.
[64] Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088–2091.
[65] Gao, P.; Szostak, M. *Org. Lett*. **2020**, *22*, 15, 6010–6015.

Scheme 1.5: Natural Products Synthesized through Iridium-Catalyzed C-H Borylation



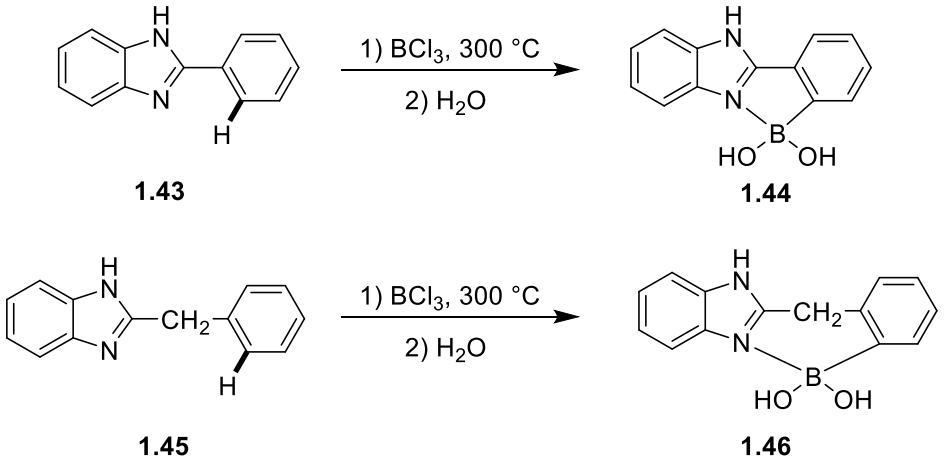
1.2.3 Metal-Free C-H Borylation using Boron Trihalides

The first example of C-H borylation using boron halides came from Dewar's initial report on azaborine synthesis in 1958. He synthesized a BN phenanthrene derivative through the reaction between 2-aminodiphenyl and boron trichloride, followed by a reduction.[14a] Similarly, in 1963, MacLean and coworkers prepared 2-(2-boronophenyl)-benzimidazole (**1.44**) and 2-(2-boronobenzyl)-benzimidazole (**1.46**) using boron trichloride. Both 2-phenylbenzimidazole (**1.43**) and 2-benzylbenzimidazole (**1.45**) were subjected to a stream of boron trichloride at 300 °C and subsequently hydrolyzed to give their respective products, **1.44** and **1.46** (Scheme 1.6).[66] Due to

[66] Letsinger, R. L.; MacLean, D. B. *J. Am. Chem. Soc*. **1963**, *85*, 2230–2236.

the success of these reactions, other works were published achieving similar chemistry[67] however, the harsh conditions required, along with a limited substrate scope, led to a lull in activity surrounding borylation through boron trihalides.

Scheme 1.6: Initial C-H Borylation using Boron Halides and Harsh Conditions[66]

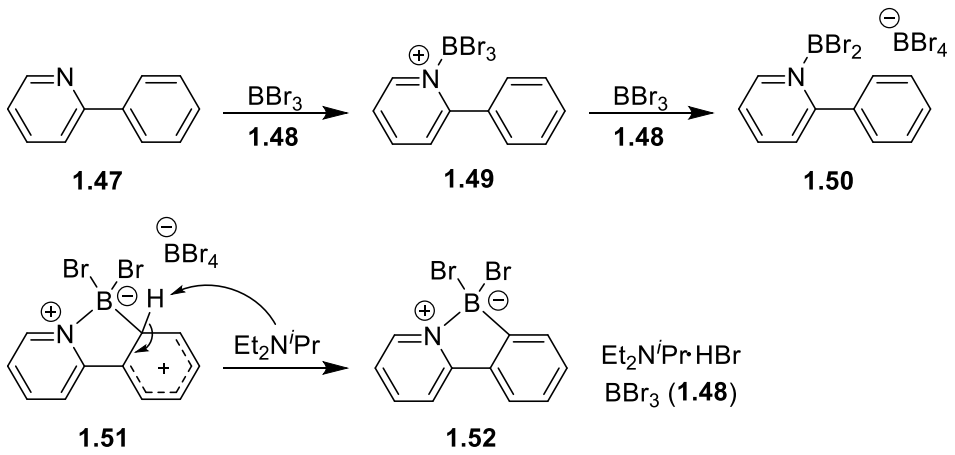


In 2010, Murakami *et al*. developed a mild borylation of 2-arylpryridines at room temperature using boron tribromide as the borylating reagent and diethylisopropylamine as the base.[68] The reaction gave pyridine–dibromoborane complexes in high yields, which could be transformed into pyridine–(dialkyl/diaryl)boranes through treatment with organometallic reagents or reduction with LAH. They were able to devise a plausible mechanism for the formation of these products (Scheme 1.7). The Lewis acidic boron of the BBr_3 (**1.48**) can coordinate to the Lewis basic nitrogen of the pyridine (**1.47**) to form complex **1.49**. A bromide is then abstracted from **1.49**

[67] (a) Koster, R.; Iwasaki, K. *Advan. Chem. Ser.* **1964**, *42*, 148. (b) Koster, R.; Iwasaki, K. *Chem. Abstr.*, **1964**, *60*, 10705.
[68] Ishida, N.; Moriya, T.; Goya, T.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 8709–8712.

by another BBr_3 to afford the borenium ion[69] (**1.50**). The electrophilic borenium ion then attacks the corresponding aromatic ring to yield the Wheland intermediate[70] (**1.51**). Finally, base assisted loss of the proton rearomatizes the ring and furnishes the desired product (**1.52**).[68]

Scheme 1.7: Plausible Mechanism for the Borylation of 2-arylpyridines using BBr_3[68]

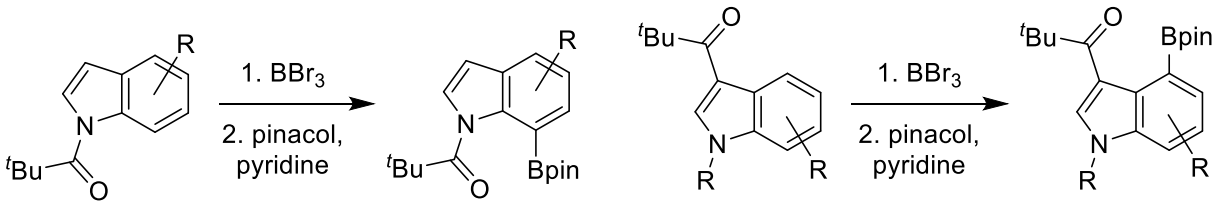


Recently, Shi *et al*. and Ingleson *et al*. both published metal-free, acyl-directed borylations using boron tribromide.[71,72] Shi demonstrated how using an acyl directing group in conjunction with BBr_3 allows for the borylation of various substituted indole moieties at both the C7- and C4-positions as well as different heteroarenes. The reactions were carried out at room temperature and subsequently reacted with pinacol and pyridine to afford the Bpin functional group (Scheme 1.8, top). To show the application of their reaction, they conducted a cascade C-H boryation/C-C and C-Het bond formation through Suzuki-Miyuara cross coupling to form different natural products. Similarly, Ingleson borylated indole moieties at the C7-position using an acyl directing group, but

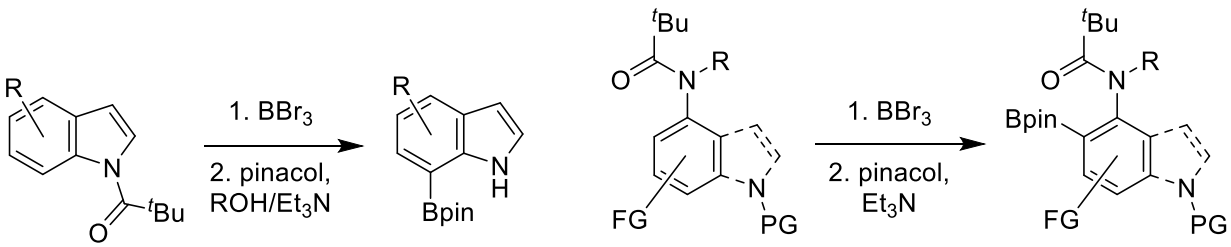
[69] (a) Ryschkewitsch, G. E.; Miller, V. R. *J. Am. Chem. Soc.* **1973**, *95*, 2836-2839. (b) Kolle, P.; Noth, H. *Chem. Rev.* **1985**, *85*, 399–418. (c) Piers, W. E.; Bourke, S. C.; Conroy, K. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 5016–5036. (d) Chiu, C.-W.; Gabbai, F. P. *Organometallics* **2008**, *27*, 1657–1659.
[70] Wheland, G. W. *J. Am. Chem. Soc.*, **1942**, *64*, 900–908.
[71] Shi, Z.; et. al. *Nature* **2019**, *575*, 336–340.
[72] Iqbal, S. A.: Cid, J.; Procter, R. J.; Uzelac, M.; Yuan, K.; Ingleson, M. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 15381–15385.

could also achieve *ortho*-borylation of aniline derivatives. Conversely, some of the reactions needed to be heated to 60 °C in order to achieve significant borylation. They were also able to remove the *N*-pivaloyl group of the indole via the addition of methanol in the second step and heating to 60 °C (Scheme 1.8, bottom). These two examples of metal-free C-H borylation of heteroarenes were the inspiration for the development of our new method (*vide infra*).

Scheme 1.8: Recent Metal-Free Directed C-H Borylations using BBr_3[71,72]



Shi 2019



Ingleson 2019

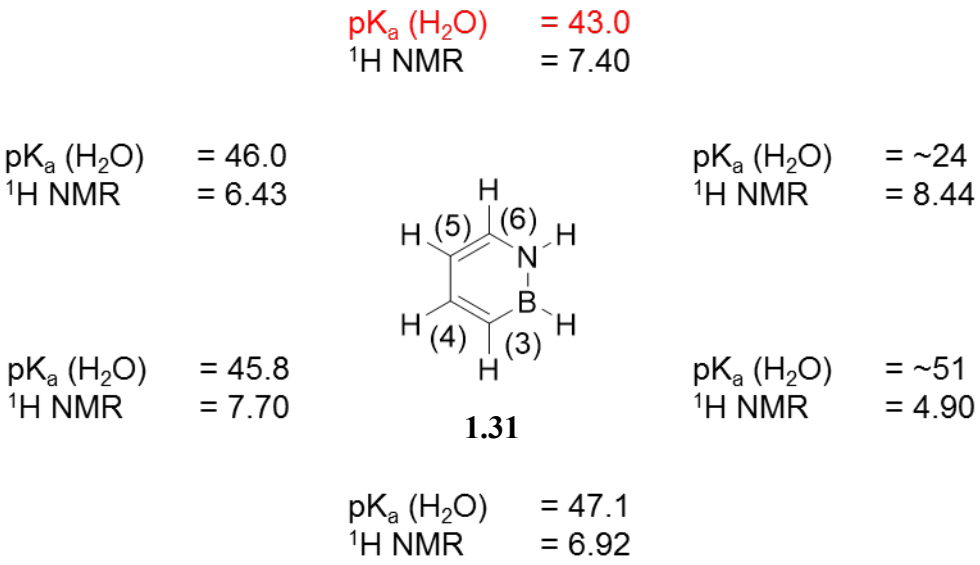
1.3 Direct Borylation of Azaborines

1.3.1 Background

It has been demonstrated that BN-arenes are capable of undergoing C-H borylation as well.[38] The lack of symmetry present in the azaborines leads to unique reactivity of each position of the carbon backbone. The distinction in chemical character allows for site selective borylation to occur. The C3-position is the least acidic, but due to resonance of the azaborine, it has a partial negative charge and is the most electron rich carbon, allowing for it to undergo electrophilic aromatic substitution reactions (EAS).[43] This is also consistent with its upfield shifted NMR signal.[5d] C4 has the most downfield proton, which is typical of protons that undergo C-H activation in borylation reactions. Similar to C3, C5 has a partial negative charge due to resonance and can readily undergo EAS reactions. Finally, C6 is the most acidic position of the carbon backbone with a pK_a of 43 making it easier to undergo borylation reactions (Figure 1.9, calculated pKa (B3LYP/DZVP2) values in H_2O, G3MP2 bond dissociation energies (BDE) for the corresponding C−H bonds).[37] It has been shown that depending on the substitution patterns, borylation can occur at the C4-, C5- and C6-positions.[38,73]

[73] McConnell, C. R.; Haeffner, F.; Baggett, A. W.; Liu, S.-Y. *J. Am. Chem. Soc*. **2019**, *141*, 9072–9078.

Figure 1.9: NMR Shifts and pKa's of each Hydrogen Around the Parent 1,2-Azaborine[21, 38]



1.31

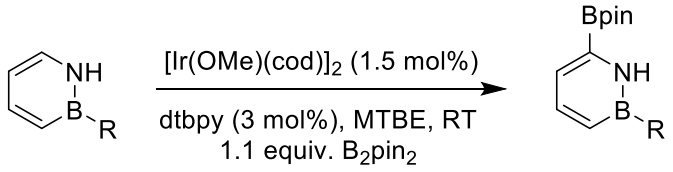
1.3.2 Iridium Catalyzed C-H Borylation of C6

When testing iridium catalyzed C-H borylation conditions on *B*-substituted 1,2-azaborines, it was found that borylation occurs at the site of the most acidic proton, the C6-position.[38] This selectivity is also consistent with the observation that C-H borylation of nitrogen-containing heteroarenes occurs alpha to the nitrogen.[60] The functionalization at C6 was of particular interest because it could allow for the access of new κ^2-N,N-bidentate ligands through Suzuki cross coupling.

Various *B*-substituted 1,2-azaborines were reacted with the (1,5-cod)(methoxy)iridium (I) dimer in the presence of 4,4'-di-tert-butyl-2,2'-bipyridine (dtbpy) and bis(pinacolato)diboron (B_2pin_2) to afford the desired C6 borylated product as a single regioisomer. This reaction could

tolerate various functional groups on the 1,2-azaborine boron including aryl, alkyl,[74] and an alkoxide group (Table 1.3).[38] Further substitution could also be tolerated at the C3 position as well.[75]

Table 1.3: Substrate Scope for C-H Borylation of 1,2-Azaborine



entry	substrate	product	yield (%)
1	**1.31** (R = H)	**2.31**	71
2	**1.53** (R = Me)	**2.53**	67
3	**1.54** (R = *n*-Bu)	**2.54**	86
4	**1.55** (R = Ph)	**2.55**	75
5	**1.56** (R = Mes)	**2.56**	92
6	**1.57** (R = O-*n*-Bu)	**2.57**	66

Once the borylated products were in hand, they could be subjected to Suzuki cross coupling conditions to install various arenes and heteroarenes. Furthermore, these new azaborines containing nitrogen heteroarenes had the potential to act as novel κ^2-N,N-bidentate ligands.

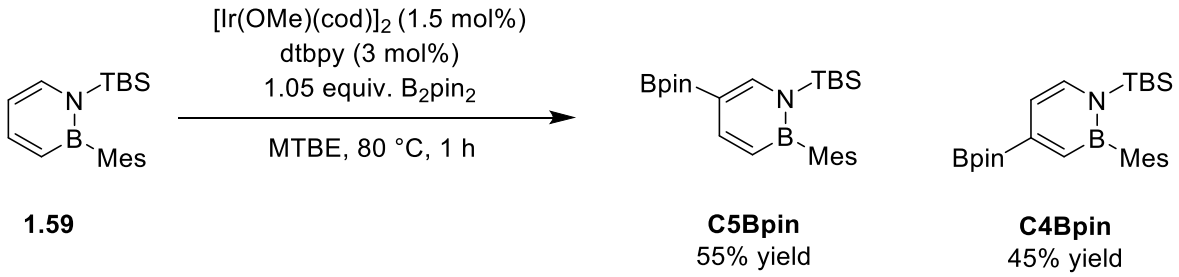
1.3.3 Unselective Borylation with Iridium Catalyst

Besides selective C6 borylation, it was found that *N,B*-disubstituted 1,2-azaborines could also be borylated at the C5- and C4-positions using similar conditions. Reacting *N*-TBS, *B*-Mes-1,2-azaborine (**1.59**) with the (1,5-cyclooctadiene)(methoxy)iridium (I) dimer in the presence of

[74] Baggett, A. W.; Liu, S.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 15259–15264.
[75] Baggett, A. W.; Guo, F.; Li, B.; Liu, S.-Y.; Jakle, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 11191–11195.

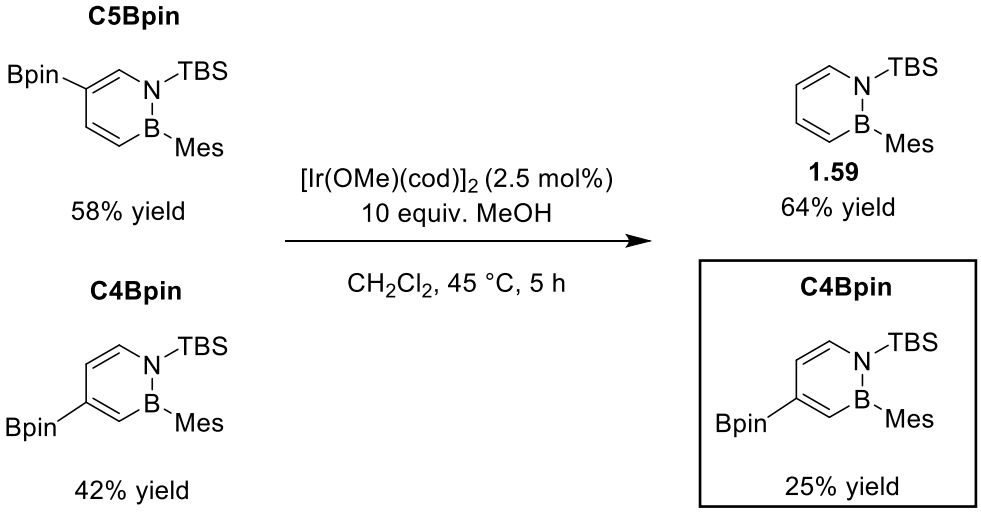
4,4'-Di-tert-butyl-2,2'-bipyridine (dtbpy) and bis(pinacolato)diboron (B_2pin_2) yields a mixture of 1 to 1.2-1.4 C4- and C5-borylated regioisomers (**C5Bpin** and **C4Bpin**) (Scheme 1.9).[73]

Scheme 1.9: C4- and C5-Borylation of *N*-TBS, *B*-Mes-1,2-Azaborine[73]



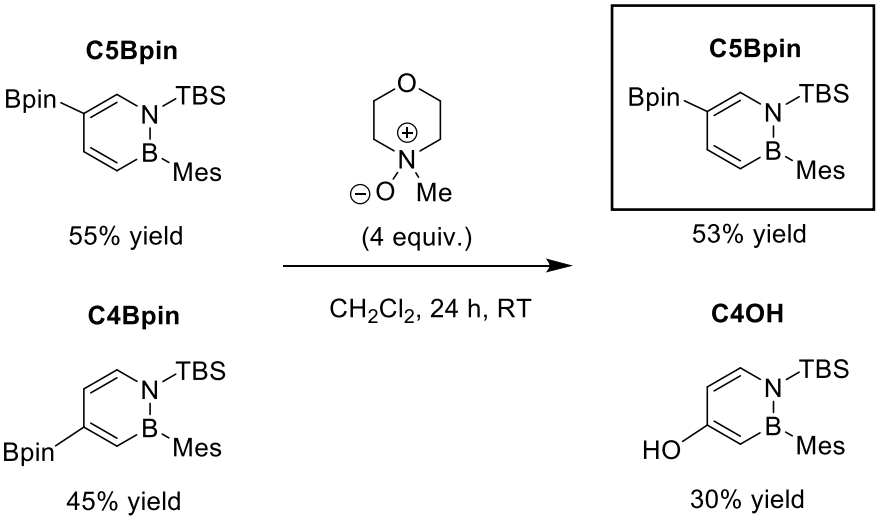
However, in order to be able to utilize these new building blocks, they had to be isolated as single products. To achieve this, kinetic resolution was required. To isolate **C4Bpin**, the mixture is subjected to the iridium dimer catalyst in the presence of methanol to yield the desired product in 25% yield with starting material (**1.59**) as byproduct (Scheme 1.10). This method is successful because the C5-position has stronger nucleophilic character so it favors transition-metal mediated protodeborylation.

Scheme 1.10: Kinetic Resolution using an Iridium Catalyst to Isolate C4Bpin



Additionally, to afford the C5 borylated product, the mixture reacted with NMO to yield isolated **C5Bpin** in 53% yield with **C4OH** as the byproduct (Scheme 1.11). This reaction could successfully act as a kinetic resolution because the rate of NMO oxidation with **C4Bpin** was 29 times faster than the decomposition of **C5Bpin** in the presences of NMO.

Scheme 1.11: Kinetic Resolution using NMO to Isolate C5Bpin



The importance of isolating both **C4Bpin** and **C5Bpin** was demonstrated by the fact that they could undergo Suzuki-Miyaura cross-coupling with various aryl halides and act as building blocks for more complex molecules.

1.4 Metal-Free Selective Borylation of C5

1.4.1 Introduction

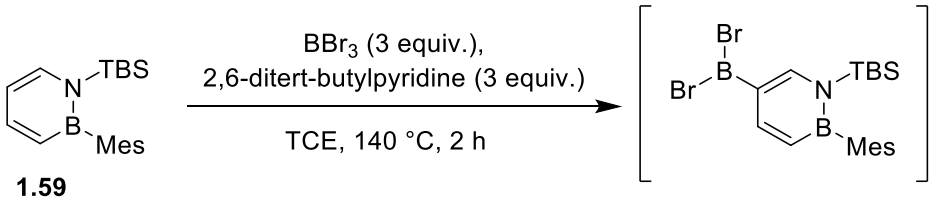
While borylation can occur selectively at C6 and unselectively at both C4- and C5-positions with the use of an iridium catalyst, there has yet to be a method in which the C5-position of the azaborine can be selectively functionalized. Herein, we report the successful development of a method to selectively borylate the C5-position with no need for a kinetic resolution, transition metal, or directing group.

1.4.2 Initial Discovery and Optimization

Literature precedent for this new reaction came from the Shi and Ingelson papers that were recently published.[71,72] When implementing similar conditions with our azaborine, it was observed that borylation occurred selectively at the C5-position without the need for a directing group. In order to fully exploit this reactivity, various conditions were tested to afford C5-substitution as the product.

We chose *N*-TBS, *B*-Mes-1,2-azaborine (**1.59**) as our model reactant to optimize the borylation conditions. It was found that reacting **1.59** with 3 equivalents of BBr_3 and 3 equivalents of 2,6-ditertbutylpyridine (DTBP) in tetrachloroethane (TCE) at 140 °C for 2 hours, the reaction yielded 90% C5-borylated product (Table 1.4, entry 1). We tested different boron reagents and saw no product formation with either BCl_3 or $BF_3{\cdot}OEt_2$ (entries 2-3). Use of different solvents led to a diminished yield (entries 4-5) and similarly, changing the base also led to no product formation (entries 6-7) suggesting that a bulky, non-nucleophilic base was necessary. Upon lowering the temperature, a decrease in yield was observed consistent with the reaction proceeding slower than at an elevated temperature (entries 8-9). Finally, it can be seen that with less equivalents of base or BBr_3, the yield is decreased. (entries 10-12). The most dramatic decrease in yield can be seen when the equivalents of BBr_3 is changed from 2 equivalents to 1. This result is consistent with the BBr_3 molecules first disproportionating to form the more reactive borenium cation before undergoing attack by the azaborine. This mechanism is consistent with previously reported reactions using BBr_3 (*vide supra*).[68]

Table 1.4: Optimization Scope for C5-Borylation Reaction



entry	deviation	yield (%)[a]
1	none	90 (83)
2	BCl_3 instead of BBr_3	0
3	$BF_3{\cdot}OEt_2$ instead of BBr_3	0
4	toluene as the solvent	65
5	bromobenzene as the solvent	76
6	Et_3N instead of DTBP	0
7	2,6-lutidine instead of DTBP	0
8	Reaction temperature 80 ˚C	59
9	Reaction temperature 50 ˚C	40
10	DTBP (2 equiv.)	65
11	BBr_3 (2 equiv.)	83
12	BBr_3 (1 equiv.)	27

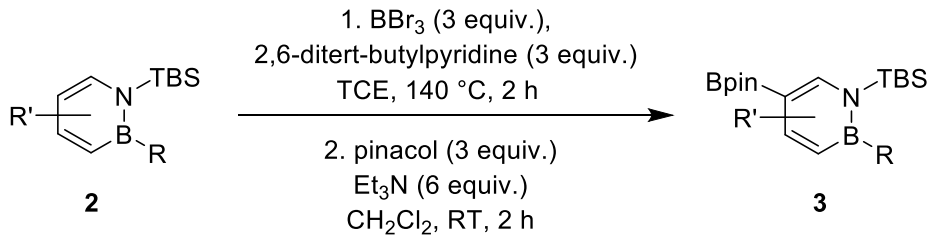
[a]NMR yield (Isolated yield as the Bpin derivative in parentheses)

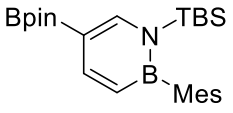
1.4.3 Substrate Scope

With the optimized conditions in hand, different substrates were tested to identify the scope of the reaction. The model substrate **3a** could be isolated in up to 83% yield as the Bpin derivative. Further substitution could be tolerated at the C3 position affording the tetra-orthogonal azaborine (Table 1.5, **3b**). Various substituents on the boron could also be tolerated under these conditions (Table 1.5, **3c-f**). However, when a chloro group was present on the boron, the intermediate could not be trapped with pinacol due to the reactivity of the *B*-Cl bond so only an NMR yield is reported. Additionally, when a phenyl ring is attached to the boron of the azaborine, a mixture of

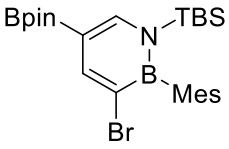
monoborylated C5 and monoborylated C3 isomers is isolated in an 80:20 ratio. When allowed to run for longer, the diborylated product, **3e**, can be isolated cleanly.

Table 1.5: Substrate Scope for C5-Borylation Reaction

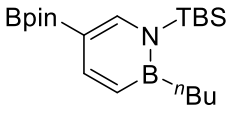




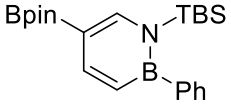
3a, 83%



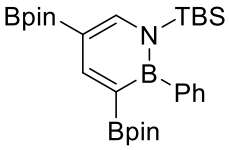
3b, 65%



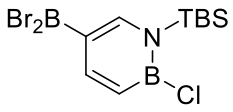
3c, 59%



3d, 55%[a]



3e, 42%[b]

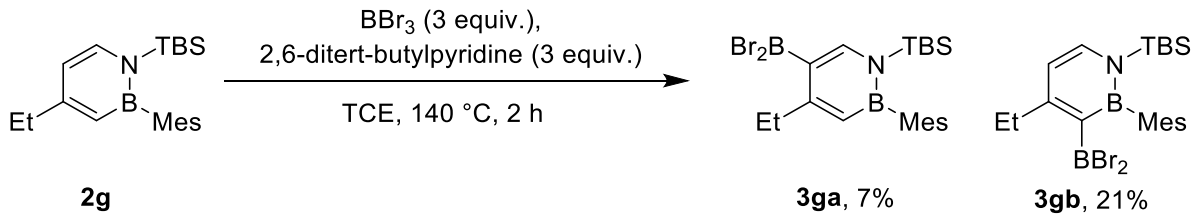


3f, 52%[c]

[a]mix C3/C5-monoborylated product 80:20, [b]Bisborylated product, 5 h, [c]NMR yield

It was found that when **3a** was resubjected to the standard conditions, no borylation occurred at the C3 position. This suggests that in the presence of a boronate ester group, the BBr_3 is consumed by converting the Bpin group into the BBr_2 intermediate, resulting in an insufficient amount of BBr_3 to add to the C3 position. However, it is expected that a different substituent at C5 would be tolerated and lead to C3 borylation. It was also found that when an ethyl group is present at the C4-position, **2g**, a mixture is obtained with 7% C5- and 21% C3- borylated BN heterocycle by NMR (Scheme 1.12, see SI for analysis).

Scheme 1.12: C4-Substituted Product

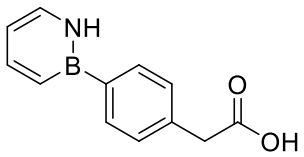


2g **3ga**, 7% **3gb**, 21%

1.4.4 Synthesis of BN-Felbinac

To demonstrate the applications of this reaction, we sought out to synthesize a biphenyl drug molecule. We chose to focus our attention on biphenyl systems because they are considered privileged motifs in medicinal chemistry.[30] We decided to synthesize the BN-isostere of Felbinac, a nonsteroidal anti-inflammatory drug (NSAID), which is used to treat muscle inflammation and arthritis.[76] We have previously synthesized a BN-Felbinac analogue where the only substitution on the azaborine stems from the boron atom[77] (Figure 1.10).

Figure 1.10: Previously Synthesized BN-Felbinac Analogue



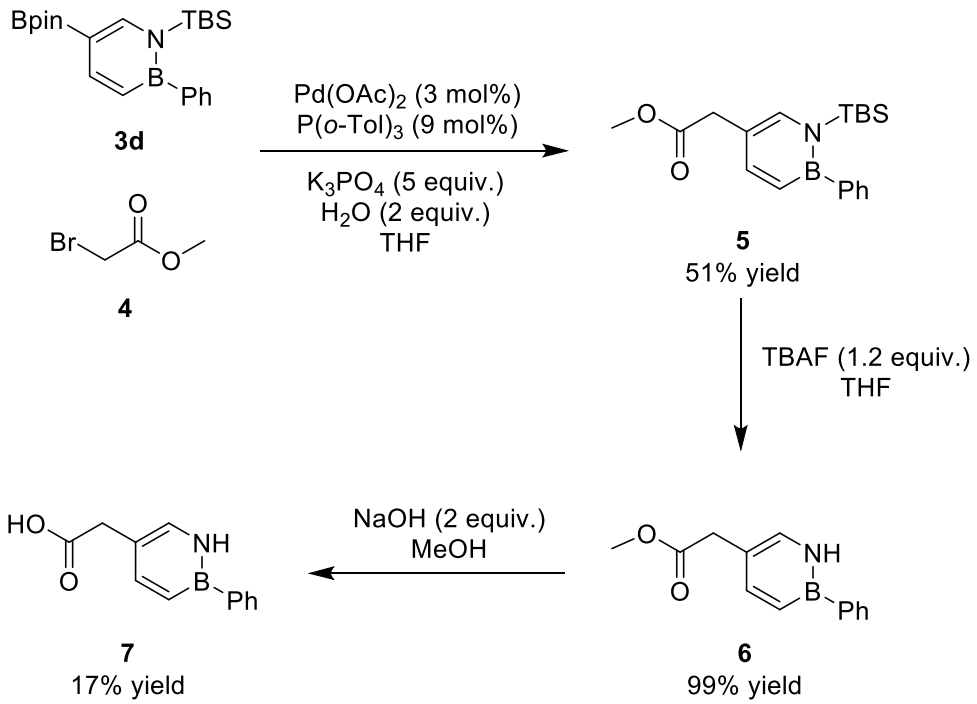
BN-Felbinac 1

Scheme 1.13 illustrates the synthetic route taken to synthesize our new BN-Felbinac analogue. Previously reported cross coupling techniques were tested using azaborines and it was

[76] Walsh, D. A.; Shamblee, D.A.; Welstead, W. J.; Sancilio, L.F. *J. Med. Chem.* **1982**, *25*, 446–451.
[77] Rudebusch, G. E.; Zakharov, L. N.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 9316–9319.

found that the use of $Pd(OAc)_2$[78] as the Pd precursor was suitable to successfully cross couple the azaborine mixture **3d** with commercially available bromoacetate (**4**) to produce compound **5** in moderate yield (51%). Compound **5** was then deprotected using tetrabutylammonium fluoride (TBAF) to afford **6** in quantitative yield and a subsequent saponification yielded the desired new BN-Felbinac (**7**) analogue in 17%. This dramatic decrease in yield can be attributed to the small amount **3d** at the beginning of this synthetic route as well as having to repeat the saponification conditions in order for the reaction to go to completion. Future studies should be able to attain a much higher yield.

Scheme 1.13: Total Synthesis of BN-Felbinac



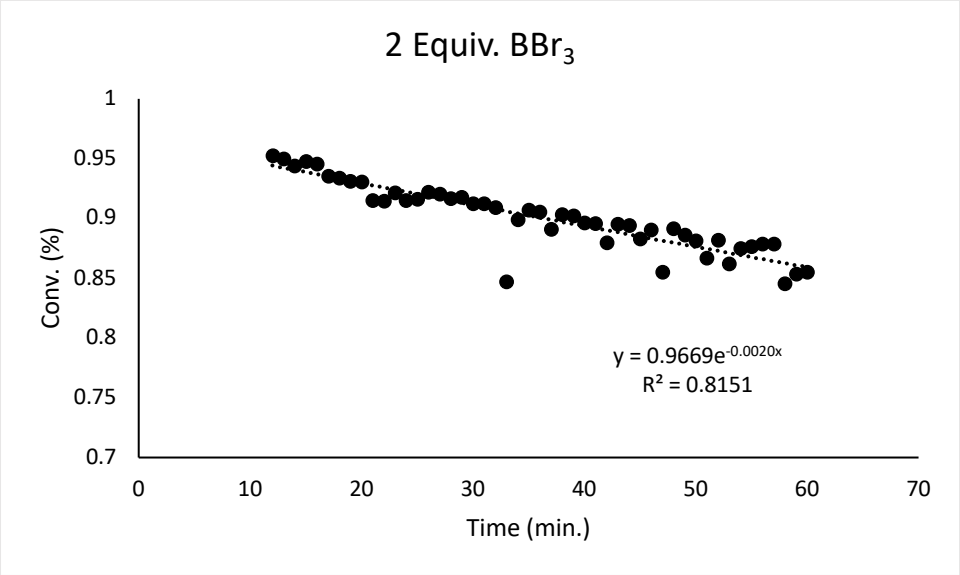
[78] Gooßen, L. J. *Chem. Commun.* **2001**, 669–670.

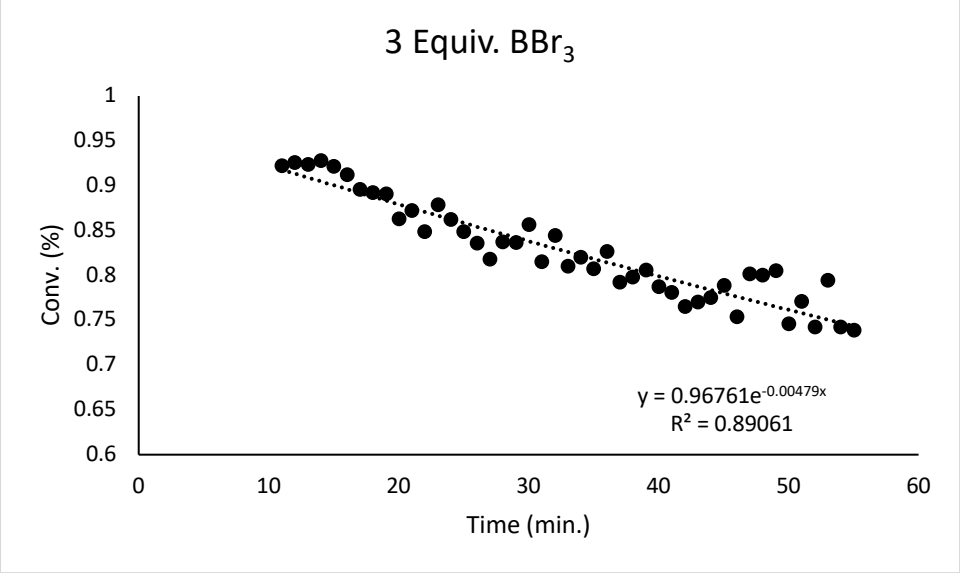
Even though **3d** was isolated as a mixture of both C5- and C3-borylated product, the cross coupling was selective for the C5-product. It was also possible to recover the pure C3-borylated product after subjecting the mixture to the cross coupling conditions. (See SI for characterization)

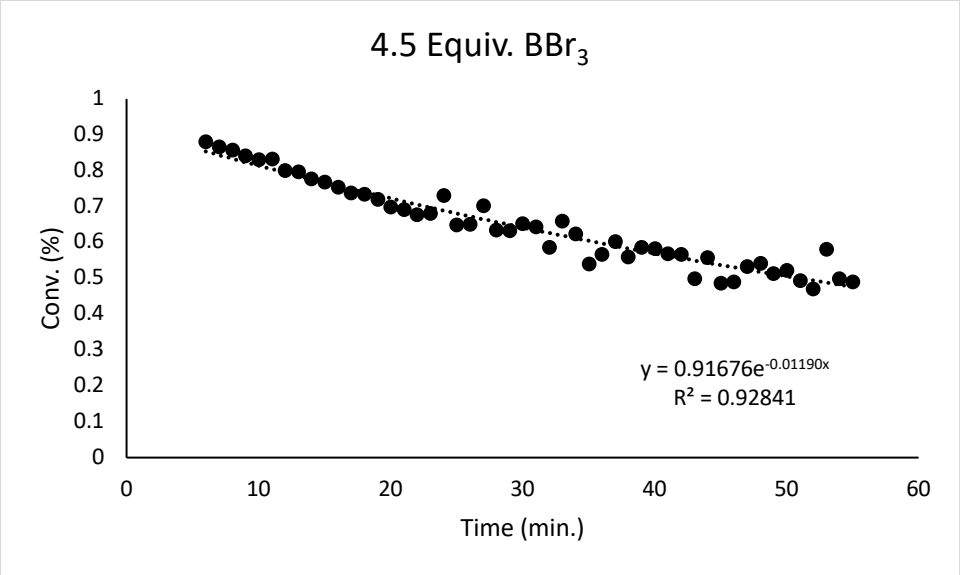
1.4.5 Mechanistic Studies

To probe the mechanistic involvement of BBr_3, various kinetic studies were performed to determine its order in the reaction. NMR experiments were done to measure the conversion versus time for three different concentrations (Figure 1.11). The concentrations selected were 0.50 M, 0.75 M and 1.13 M equating to 2, 3, and 4.5 equivalents (with one data point being below the standard conditions and one being above). The conversion versus time graphs were created by plotting the disappearance of starting material versus time measured in minutes. These graphs were then fit to an exponential decay with the exponent equal to the k_{obs} for each reaction. The log of the k_{obs} was then plotted against the log of the concentration for each reaction and the slope of the linear fit line was found to be 2.19, consistent with a second order in BBr_3.

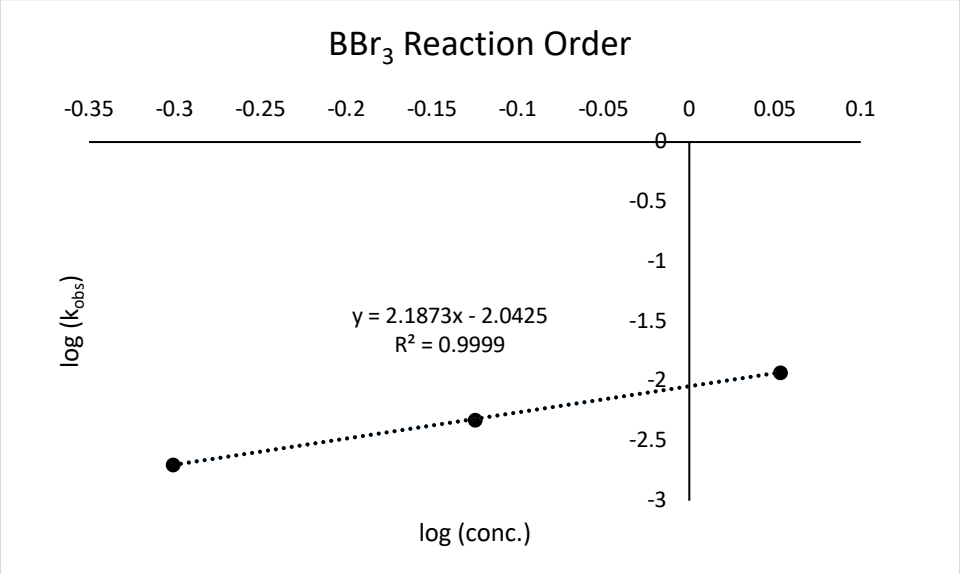
Figure 1.11: Kinetic Experiment Plots







(Conversion for each graph is defined as the disappearance of starting material)

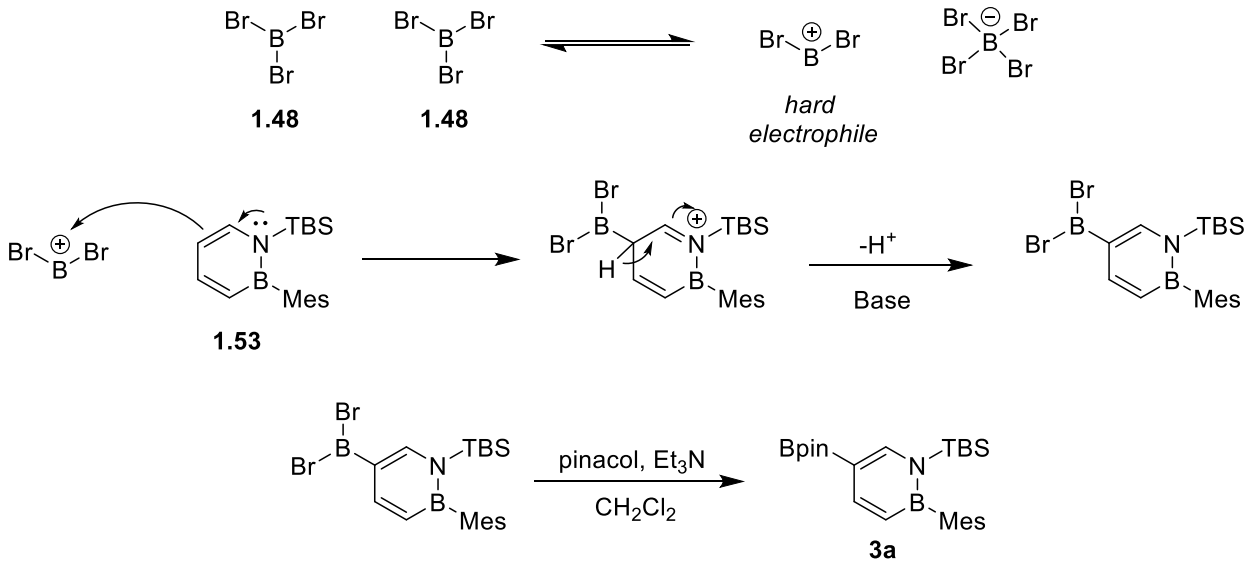


Our hypothesis is that perhaps the C5 position can be considered the more negatively charged position and is therefore a harder nucleophile that has a stronger propensity to react with the hard borenium electrophile.[79] This is in contrast to our previous work where the C3-position

[79] Jolly, W. L. Modern Inorganic Chemistry; McGraw-Hill: New York, **1984.**

reacts selectively with the soft Br_2 electrophile.[43,80] Our proposed mechanism is shown in Figure 1.12.

Figure 1.12: Proposed Mechanism for C5-Borylation



BBr_3 first disproportionates to form the borenium cation as well as the corresponding BBr_4^- anion. The lone pair on the nitrogen can then kick down and push the electrons to attack the borenium cation. The resulting intermediate undergoes base-assisted loss of a proton to rearomatize the azaborine and afford the C5-substituted intermediate. This intermediate is then trapped with pinacol to yield the desired C5-borylated product.

1.4.6 Future Directions and Conclusion

We have only scratched the surface when it comes to the importance and applications of this reaction. Future directions will allow this project to be greatly expanded in terms of substrate

[80] Brown, A. N.; Li, B.; Liu, S.-Y. *J. Am. Chem. Soc*. **2015**, *137*, 8932–8935.

scope, synthesizing many new BN-isosteres of drug molecules, as well as further functionalizing our new BN-Felbinac analogue to create a new BN-CDK2 inhibitor. This would allow for the comparison of the bioactivity of our new BN-CDK2 inhibitor to the one previously synthesized (*vide supra*).

In summary, we have developed a new, metal-free method to directly borylate the C5 position of our 1,2-azaborines. The scope of this reaction is tolerant of different substitution on the boron as well as at the C3 position of the azaborine. To demonstrate the application of this reaction, we synthesized a new BN isostere of the drug molecule felbinac. It also allows us to more fully explore the chemical space of biphenyl motifs by taking advantage of the unique reactivity of azaborines by directly functionalizing the para position of the azaborine. Mechanistic analysis suggests a second order in BBr_3 consistent with the formation of a borenium cation. Additionally, the selectivity present can most likely be explained by the hard-soft acid-base chemistry. All-in-all, this reaction greatly expands the chemical space of biphenyl motifs, while also allowing for the straight-forward functionalization of azaborines.

1.5 Experimental Section

1.5.1 General Information

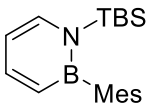
All oxygen- and moisture-sensitive manipulations were carried out in oven-dried glassware under an inert atmosphere (N_2) using either standard Schlenk technique or a nitrogen-filled glove box.

CH_2Cl_2, THF, Et_2O, and pentane were dried using a Pure Process Technology solvent purification system, which passed the solvents through a neutral alumina column under argon. CD_2Cl_2, $CDCl_3$, C_6D_6 and $C_2D_2Cl_4$ were purified by distillation after drying over calcium hydride and degassed through a freeze-pump-thaw technique. All other reagents were purchased from commercial vendors (Acros Organics®, Millipore Sigma®, Oakwood Chemical®, or Combi-Blocks®) and used as received unless otherwise stated.

^{1}H, ^{11}B, and ^{13}C spectra were recorded on a Varian VNMRS 600 MHz, VNMRS 500 MHz, INOVA 500 MHz, or VNMRS 400 MHz spectrometer at both ambient temperature and 50 °C. ^{1}H NMR spectra were internally referenced to chloroform-d (δ 7.26 ppm), methylene chloride-d2 (δ 5.32 ppm), benzene-d6 (δ 7.16 ppm) or tetrachloroethane-d2 (δ 6.00 ppm). ^{11}B NMR spectra were externally referenced to BF_3•Et_2O (δ 0.0 ppm).

Infrared spectroscopy was performed on a Bruker ALPHA-Platinum FT-IR Spectrometer with an ATR-sampling module on OPUS software. High-resolution mass spectrometry data were obtained at the Boston College mass spectrometry facility on a JEOL AccuTOF instrument (JEOL USA, Peabody, MA) equipped with a DART ion source (IonSense, Inc., Danvers, MA) in positive ion mode.

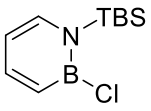
1.5.2 Syntheses



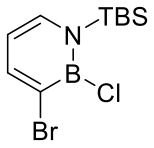
1.59

Compound **1.59** (2.13 g, 78% yield) was synthesized as a colorless oil from *N*-TBS, *B*-Cl 1,2-azaborine **1.27** (**1.27** was prepared according to literature procedures[21]) and 2-mesityllithium in THF. A 20 mL vial was charged with **1.27** (2.00 g, 8.79 mmol) and tetrahydrofuran (16.0 mL) under nitrogen. To the flask was then added (2,4,6-trimethylphenyl)lithium (2.22 g, 17.6 mmol) slowly over 7 minutes. After the addition, the reaction mixture was allowed to stir for an hour at room temperature. The crude mixture was dissolved in ethyl acetate (2 x 20.0 mL), washed with brine (30.0 mL), dried over $NaSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography using silica in 100% hexanes to yield a single fraction. Spectra of the isolated compound matched previously published records.[38]

Compound **1.27**:

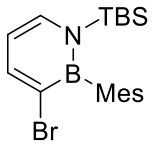


1.27



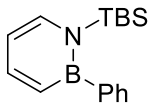
S1

Compound **S1** (857 mg, 73% yield) was synthesized as a colorless oil from compound **1.27** and a solution of molecular bromine in CH_2Cl_2. In the glovebox, an oven dried 50 mL round bottom flask equipped with a stir bar was charged with **1.27** (0.87 g, 3.8 mmol) and dissolved in CH_2Cl_2 (10.0 mL). The flask was cooled to –30 ºC using a dry ice/acetone bath, and a solution of molecular bromine (599 mg, 3.75 mmol, 192 μL) was added dropwise via a syringe to the reaction mixture. After the addition of bromine, the solution turned red-orange color. The reaction was allowed to stir for 1.25 hours, while warming to room temperature. The solution was then concentrated under reduced pressure, and the crude material was purified by vacuum distillation (100 ºC internal, 300 mTorr). Spectra of the isolated compound matched previously published records.[80]



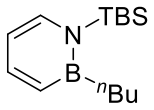
2b

Compound **2b** (330 mg, 30% yield) was synthesized as an off-white solid from compound **S1** and 2-mesityllithium. In the glove box, compound **S1** (857 mg, 2.79 mmol) was dissolved in Et_2O (10.0 mL) at room temperature. Solid 2-mesityllithium (705 mg, 5.59 mmol) was added in portions to the stirred solution at room temperature. The reaction mixture was allowed to stir for 3 hours at room temperature, at which point 11B NMR analysis deemed the reaction to be complete. The solution was then concentrated under reduced pressure and 40 mL pentane was added. The resulting mixture was poured into 50.0 mL H_2O, and the organic components were extracted with hexanes (3 x 50.0 mL). The combined organic layers were washed with brine, dried over $NaSO_4$, passed through a fritted funnel, and concentrated under reduced pressure. The residue was reconstituted in a minimal amount of pentane and run through a silica gel column using 100% pentane until the product was observed on TLC, then 2% diethyl ether in hexanes was used to obtain the desired product. Spectra of the isolated compound matched previously published records.[75]



2d

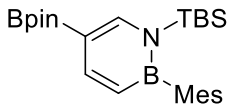
Compound **2d** (1.29 g, 54% yield) was synthesized as a colorless oil from compound **1.27** and phenyl magnesium bromide in THF. In the glovebox, a 100 mL round-bottom flask equipped with a stir bar was charged with **1.27** (2.00 g, 8.79 mmol) and THF (20.0 mL). A 3.0 M solution of phenyl magnesium bromide (3.66 mL, 11.0 mmol, 1.25 equiv.) was added dropwise via a syringe in glove box and reaction mixture was allowed to stir for 12 hours at room temperature. At the conclusion of the reaction, solvent was removed under reduced pressure, and the product was purified by a plug of silica gel chromatography in the glovebox, with pentane as the eluent to yield a single fraction. Spectra of the isolated compound matched previously published records.[77]



2c

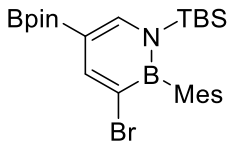
Compound **2c** (500 mg, 87% yield) was synthesized as a light brown oil from compound **1.27** and n-butyllithium in ether. In the glovebox, to a 20 mL vial was added a magnetic stir bar, **1.27** (500 mg, 2.20 mmol) and diethyl ether (5.00 mL). The vial was then transferred to a fume hood and cooled to –78 °C in a dry ice/acetone bath before *n*-butyllithium (2.50 M, 0.967 mL, 2.42 mmol) was added to the solution dropwise via a syringe. Once the addition was complete, the reaction was allowed to stir for 3 hours at room temperature. At the conclusion of the reaction, volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography in the glovebox using 2% diethyl ether/pentane to yield the desired product. Spectra of the isolated compound matched previously published records.[81]

[81] Abbey, E. R.; Lamm, A. N.; Baggett, A. W.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 12908-12913.



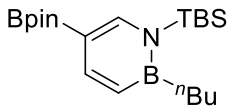
3a

In the glovebox, to an oven dried pressure vial was added **1.59** (100 mg, 321 μmol), BBr_3 (241 mg, 964 μmol, 91.4 μL) and 2,6-ditert-butylpyridine (184 mg, 964 μmol, 208 μL), all in tetrachloroethane (642 μL). The mixture was allowed to stir while refluxing at 140 °C for 2 hours. At the conclusion of the reaction, the mixture was cooled to –30 °C before a solution of 2,3-dimethylbutane-2,3-diol (114 mg, 964 μmol) and diethylethanamine (195 mg, 1.93 mmol, 269 μL) was added dropwise and allowed to stir for 2 hours at room temperature. The resulting mixture was washed with sodium bicarbonate and the organic layer was dried over $NaSO_4$. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 100% hexanes to 10% hexanes/diethyl ether to yield compound **3a** (121 mg, 276 μmol, 86% yield). Spectra of the isolated compound matched previously published records.[73]



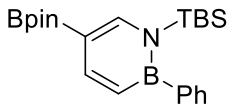
3b

In the glovebox, to an oven dried pressure vial was added **2b** (120 mg, 308 μmol), BBr_3 (231 mg, 923 μmol, 87.5 μL) and 2,6-ditert-butylpyridine (176 mg, 923 μmol, 199 μL), all in tetracholorethane (615 μL). The mixture was allowed to stir while refluxing at 140 °C for 2 hours. At the conclusion of the reaction, the mixture was cooled to –30 °C before a solution of 2,3-dimethylbutane-2,3-diol (109 mg, 923 μmol) and N,N-diethylethanamine (187 mg, 1.85 mmol, 257 μL) was added dropwise and allowed to stir for 2 hours at room temperature. The resulting mixture was washed with sodium bicarbonate and the organic layer was dried over $NaSO_4$. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 100% hexanes to 10% hexanes/diethyl ether to yield compound **3b** (108 mg, 209 μmol, 68% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 1.0 Hz, 1H), 7.98 (d, J = 1.0 Hz, 1H), 6.78 (s, 2H), 2.29 (s, 3H), 2.05 (s, 6H), 1.31 (s, 12H), 0.92 (s, 9H), -0.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 1478.0, 147.2, 138.8, 137.0, 126.9, 83.6, 27.4, 24.8, 22.7, 21.3, 19.2, -3.2. (3 carbon-boron signals are not observed). ^{11}B NMR (192 MHz, $CDCl_3$) δ 40.02, 30.43. FTIR (thin film) ν cm^{-1} = 2963, 2932, 2859, 1601. HRMS (DART) calcd for $C_{25}H_{40}B_2NO_2SiBr$ ($[M+H]^+$) 516.22706, found 516.22639.



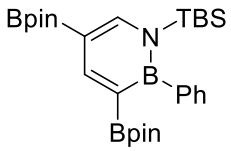
3c

In the glovebox, to an oven dried pressure vial was added **2c** (100 mg, 401 μmol), BBr_3 (302 mg, 1.20 mmol, 114 μL) and 2,6-ditert-butylpyridine (230 mg, 1.20 mmol, 260 μL), all in tetrachloroethane (802 μL) The mixture was allowed to stir and refluxed at 140 °C for 2 hours. At the conclusion of the reaction, the mixture was cooled to –30 °C before a solution of 2,3-dimethylbutane-2,3-diol (142 mg, 1.20 mmol) and N,N-diethylethanamine (244 mg, 2.41 mmol, 335 μL) was added dropwise and allowed to stir for 2 hours at room temperature. The resulting mixture was brought into the wet box and washed with sodium bicarbonate before the organic layer was dried over $NaSO_4$. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 100% pentane to 5% pentane/diethyl ether to yield compound **3c** (91.6 mg, 244 μmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.83 – 7.78 (m, 1H), 6.74 (d, J = 11.1 Hz, 1H), 1.58 – 1.47 (m, 2H), 1.42 – 1.33 (m, 2H), 1.29 (s, 12H), 1.24 – 1.17 (m, 2H), 0.95 – 0.85 (m, 12H), 0.50 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 146.4, 129.0 (br), 83.0, 29.7, 26.7, 26.1, 24.8, 21.6 (br), 19.0, 14.2, -1.4. (1 carbon-boron signal is not observed). ^{11}B NMR (128 MHz, $CDCl_3$) δ 43.55, 32.06. FTIR (thin film) ν cm^{-1} = 2955, 2929, 2858, 1604. HRMS (DART) calcd for $C_{20}H_{40}B_2NSiO_2$ ($[M+H]^+$) 376.30089, found 376.30304.



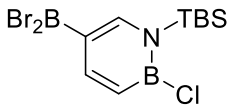
3d

In the glovebox, to an oven dried pressure vial was added **2d** (200 mg, 743 μmol), BBr_3 (558 mg, 2.23 mmol, 211 μL) and 2,6-ditert-butylpyridine (426 mg, 2.23 mmol, 482 μL), all in tetrachloroethane (1.49 mL). The mixture was allowed to stir while refluxing at 140 °C for 2 hours. At the conclusion of the reaction, the mixture was cooled to –30 °C before a solution of 2,3-dimethylbutane-2,3-diol (263 mg, 2.23 mmol) and N,N-diethylethanamine (451 mg, 4.46 mmol, 621 μL) was added dropwise and allowed to stir for 2 hours at room temperature. The resulting mixture was brought into the wet box, washed with sodium bicarbonate, and the organic layer was dried over $NaSO_4$. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 100% pentane to 5% pentane/ether to yield compound **3d** (162 mg, 411 μmol, 55% yield as a mixture of C5- and C3- borylated compounds with C3-borylated product as a minor impurity. Only the signals of the desired monoborylated compound are reported). 1H NMR (400 MHz, CD_2Cl_2) δ 7.99 (s, 1H), 7.85 (dd, J = 10.9, 1.2 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.28 (dt, J = 4.5, 2.8 Hz, 3H), 6.60 (d, J = 10.8 Hz, 1H), 1.32 (s, 12H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 147.0, 131.8, 126.7, 83.2, 29.9, 26.8, 22.7, 18.9, -2.1 (3 carbon-boron signals are not observed). ^{11}B NMR (128 MHz, $CDCl_3$) δ 41.04, 32.48. FTIR (thin film) ν cm^{-1} = 2998, 2974, 2959, 2927, 2857, 1600. HRMS (DART) calcd for $C_{22}H_{36}B_2NO_2Si$ ($[M+H]^+$) 396.26959, found 396.27028.



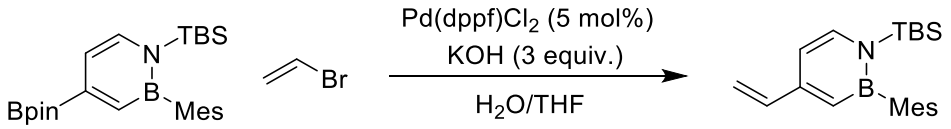
3e

In the glovebox, to an oven dried pressure vial was added **2d** (100 mg, 371.38 μmol), BBr_3 (279.12 mg, 1.11 mmol, 105.73 μL) and 2,6-ditert-butylpyridine (213.15 mg, 1.11 mmol, 240.84 μL), all in tetrachloroethane (743 μL). The mixture was allowed to stir while refluxing at 140 °C for 5 hours. At the conclusion of the reaction, the mixture was cooled to –30 °C before a solution of 2,3-dimethylbutane-2,3-diol (132 mg, 1.11 mmol) and N,N-diethylethanamine (225 mg, 2.23 mmol, 311 μL) was added dropwise and allowed to stir for 2 hours at room temperature. The resulting mixture was brought into the wet box and washed with sodium bicarbonate before the organic layer was dried over $NaSO_4$. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 100% hexane to 10% hexane/ether to yield compound **3e** (61.6 mg, 42% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.18 (s, 1H), 8.05 (s, 1H), 7.30 (dp, J = 6.1, 2.0 Hz, 2H), 7.22 (dt, J = 4.4, 1.7 Hz, 3H), 1.33 (s, 12H), 1.03 (s, 12H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 157.2, 152.6, 147.9 (br), 134.9, 128.6, 114.0 (br), 85.9, 85.0, 29.2, 27.2, 27.0, 25.0, 21.4, 16.4. (1 carbon-boron signal is not observed) ^{11}B NMR (160 MHz, CD_2Cl_2) δ 41.16, 31.92. FTIR (thin film) ν cm^{-1} = 2976, 2957, 2931, 2859, 1600, 1504. HRMS (DART) calcd for $C_{28}H_{47}B_3NO_4Si$ ($[M+H]^+$) 522.35480, found 522.35608.



3f

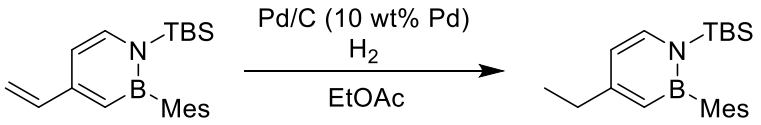
In the glovebox, to an oven dried J-young tube was added **1.27** (25 mg, 110 μmol), BBr_3 (82.6 mg, 330 μmol, 31.3 μL) and 2,6-ditert-butylpyridine (63.0 mg, 330 μmol, 71.2 μL), all in tetrachloroethane (439 μL) with 1,2-dichloroethane (10.9 mg, 110 μmol, 8.63 μL) as the internal standard. The mixture was allowed to reflux at 140 °C for 4 hours. NMR yield of reactive BBr_2 intermediate was found to be 54% yield. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.62 (d, J = 1.8 Hz, 1H), 8.15 (dd, J = 11.2, 1.7 Hz, 1H), 6.84 (d, J = 11.2 Hz, 1H), 1.01 (s, 9H), 0.69 (s, 6H).



S3 **S4**

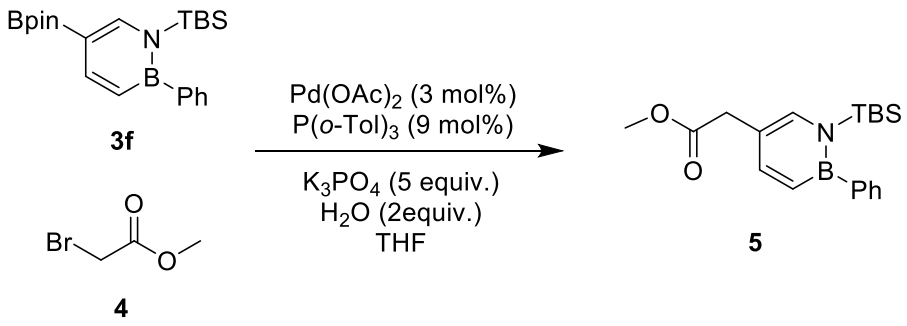
In the glovebox, a 4 mL pressure vessel was charged with **S3** (1.13 g, 2.57 mmol,), bromoethylene (1.0 M, 10.29 mL), $Pd(dppf)Cl_2$ (94.12 mg, 128.63 umol), KOH (433.04 mg, 7.72 mmol, 212.28 uL), THF (15 mL) (including from vinylBr solution) and H_2O (1.5 mL). The reaction mixture was allowed to stir at 65 °C for 1 hour. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using hexanes to yield compound **S4** (844 mg, 97% yield). Spectra of the isolated compound matched previously published records.[82]

[82] National Center for Biotechnology Information **2020**. PubChem Compound Summary for CID 132837463.

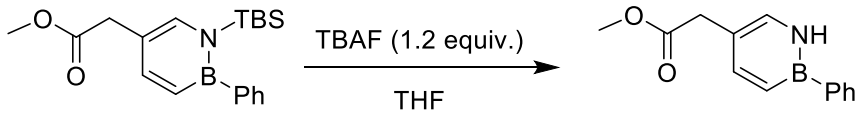


S4 **2g**

In the glovebox, a 250 mL round bottom flask was charged with **S4** (135 mg, 0.400 mmol), Pd/C (67.5 mg of 10 wt% Pd, 0.634 mmol) in ethylacetate (10 mL). The reaction mixture was allowed at room temperature under 1 atm H_2 atmosphere for 4 hours. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel chromatography using 15-40% CH_2Cl_2 in pentane as an eluent afforded the desired product **2g** (135 mg, 99%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.75 (d, J = 7.0 Hz, 1H), 6.17 (s, 2H), 5.77 (d, J = 2.1 Hz, 1H), 5.64 (dd, J = 7.0, 2.2 Hz, 1H), 1.91 (q, J = 7.5 Hz, 2H), 1.68 (s, 3H), 1.49 (s, 6H), 0.59 (t, J = 7.5 Hz, 3H), 0.31 (s, 9H), -0.62 (s, 6H). ^{11}B (160 MHz, $CDCl_3$) δ 40.13.

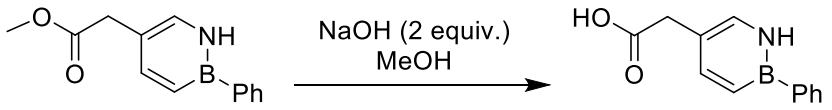


In the glovebox, to a dried pressure vial was added $Pd(OAc)_2$ (1.42 mg, 6.33 μmol), tri(o-tolyl)phosphine (P(*o*-tol)$_3$) (5.78 mg, 19.0 μmol), K_3PO_4 (224 mg, 1.05 mmol), and freshly distilled methyl 2-bromoacetate **4** (32.3 mg, 211 μmol, 19.4 μL) in THF (1.00 mL). The vial was then transferred to the wet box and degassed H_2O (7.60 mg, 422 μmol, 7.60 μL) was added. The mixture was allowed to stir for a minute before compound **3d** (100 mg, 253 μmol) in THF (1mL) was added. The mixture was then allowed to stir at 60 °C for 16 hours. At the conclusion of the reaction, the vial was brought back into the wet box and washed with degassed H_2O before being extracted with ethyl acetate and dried over $NaSO_4$. The crude material was then concentrated under reduced pressure and subjected to column chromatography in the glovebox (5% ether/pentane) to yield compound **5** (36.9 mg, 108 μmol, 51% yield). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.55 (dd, J = 11.0, 1.8 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.34 – 7.30 (m, 1H), 7.29 – 7.25 (m, 3H), 6.64 (d, J = 11.0 Hz, 1H), 3.68 (s, 3H), 3.46 (s, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.8, 137.6, 132.7, 132.0, 126.7, 116.9, 51.9, 39.1, 26.8, 18.9, -2.1. (2 carbon-boron signals are not observed) ^{11}B NMR (192 MHz, CD_2Cl_2) δ 38.56. FTIR (thin film) ν cm^{-1} = 3006, 2954, 2930, 2885, 2858, 1737, 1630. HRMS (DART) calcd for $C_{19}H_{29}BNO_2Si$ ([M+H]$^+$) 342.20551, found 342.20382.



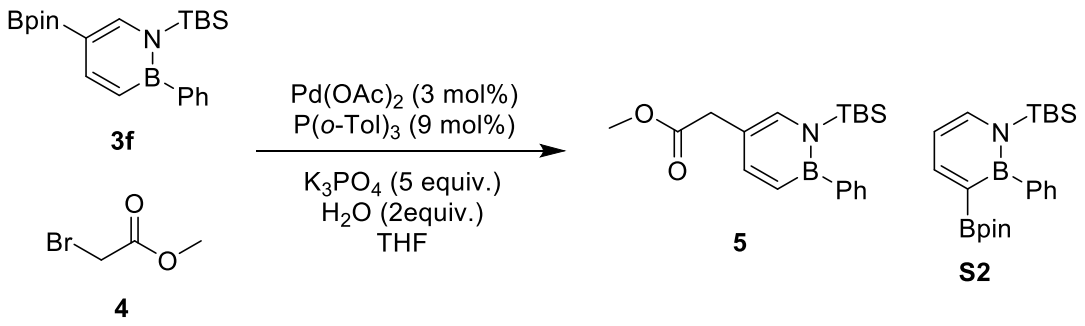
5 **6**

In the glovebox, a 20 mL vial containing a magnetic stir bar was charged with compound **5** (36.9 mg, 108 μmol) and THF (2.00 mL). A solution of tetrabutylammonium fluoride (TBAF), 1.0 M in THF (33.9 mg, 130 μmol, 37.6 μL) was added to the stirred solution and the reaction mixture was allowed to stir for 1 hour at room temperature. At the conclusion of the reaction, the mixture was concentrated under reduced pressure to yield a yellow, crude paste. The crude product was purified by silica gel chromatography in the glovebox using 4:1 ether/pentane as eluent to yield compound **6** (24.5 mg, 108 μmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.79 – 7.74 (m, 2H), 7.71 (dd, J = 11.5, 1.8 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.35 – 7.29 (m, 1H), 7.19 (dd, J = 11.4, 2.2 Hz, 1H), 3.71 (s, 3H), 3.46 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 146.6, 133.4, 132.2, 129.0, 128.1, 116.3, 52.0, 38.5. (2 carbon-boron signals are not observed) ^{11}B NMR (160 MHz, CD_2Cl_2) δ 33.25. FTIR (thin film) ν cm^{-1} = 3348, 1724, 1630, 1545. HRMS (DART) calcd for $C_{13}H_{15}BNO_2$ ($[M+H]^+$) 228.11904, found 228.11920.



6 **7**

In a glove box, a 20 mL vial was charged with a stir bar, compound **6** (24 mg, 106 μmol), NaOH (8.46 mg, 211 μmol, 3.97 μL), and MeOH (1 mL). The reaction mixture was allowed to stir for a total of 33 hours at varied temperatures (rt to 60 °C) under an inert atmosphere before removing solvent under reduced pressure. The crude solid was then redissolved in ethyl acetate and H_2O before HCl (2M) was added in dropwise until the pH reached ~2. The organic layer was then extracted with ethyl acetate and concentrated under reduced pressure to compound **7** (4 mg, 18.8 μmol, 18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.78 – 7.73 (m, 2H), 7.71 (dd, J = 11.6, 1.8 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 11.4, 2.2 Hz, 1H), 3.49 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 146.5, 133.5, 132.2, 129.1, 128.1, 115.6, 38.1. (2 carbon-boron signals are not observed) ^{11}B NMR (192 MHz, $CDCl_3$) δ 32.85. FTIR (thin film) ν cm^{-1} = 3378, 3051, 3033, 3011, 2922, 2852, 1700, 1624, 1542. HRMS (DART) calcd for $C_{12}H_{13}BNO_2$ ($[M+H]^+$) 214.10339, found 214.10372.



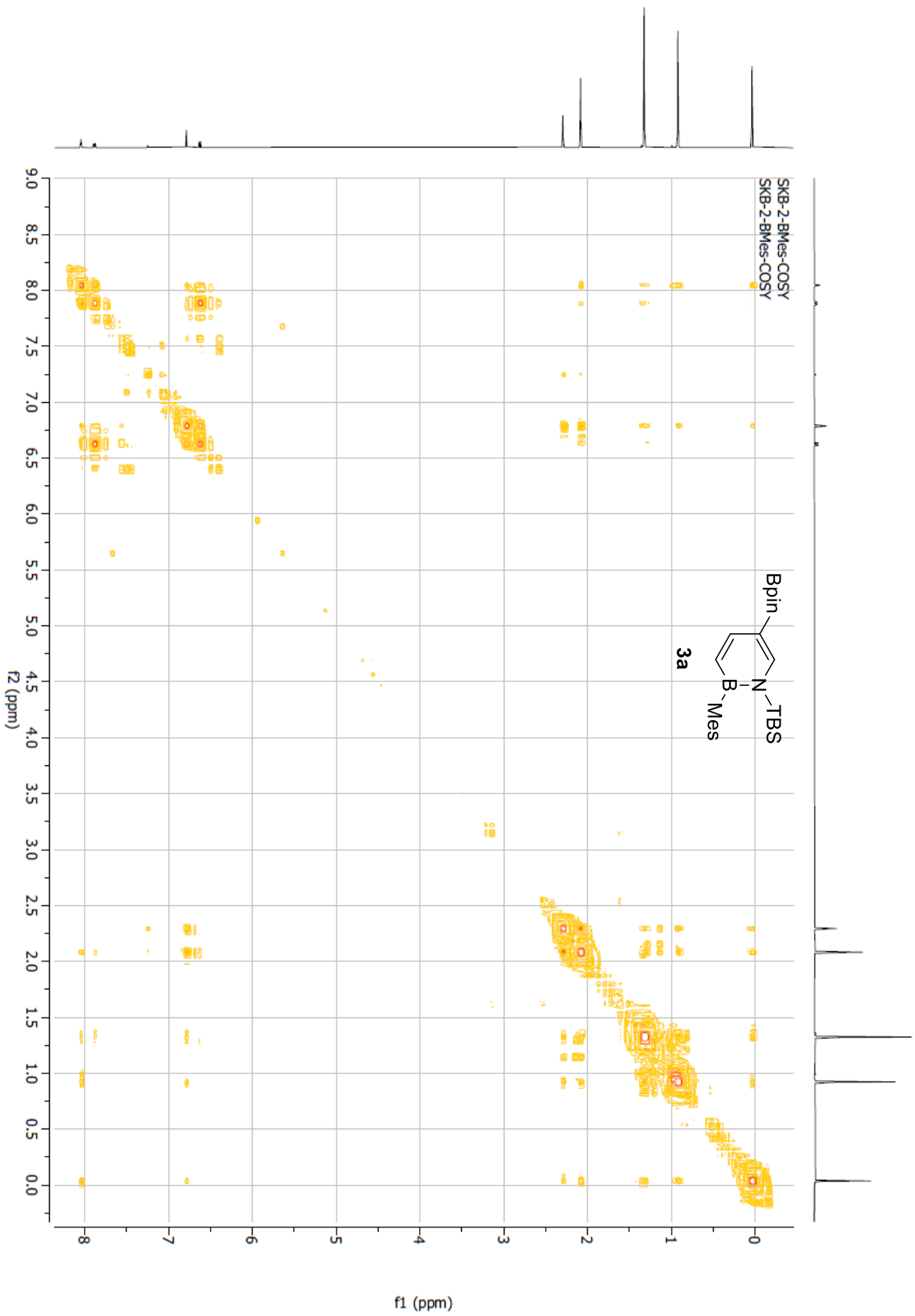
In the glovebox, to a dried pressure vial was added $Pd(OAc)_2$ (1.42 mg, 6.33 μmol), Tri(o-tolyl)phosphine (P(*o*-tol)$_3$) (5.78 mg, 19.0 μmol), K_3PO_4 (224 mg, 1.05 mmol), and freshly distilled methyl 2-bromoacetate **4** (32.3 mg, 211 μmol, 19.4 μL) in THF (1.00 mL). The vial was then transferred to the wet box and degassed H_2O (7.60 mg, 422 μmol, 7.60 μL) was added. The mixture was allowed to stir for a minute before compound **3d** (100 mg, 253 μmol) in THF (1 mL) was added. The mixture was then allowed to stir at 60 °C for 16 hours. At the conclusion of the reaction, the vial was brought back into the wet box and washed with degassed H_2O before being extracted with ethyl acetate and dried over $NaSO_4$. The crude material was then concentrated under reduced pressure and subjected to column chromatography in the glovebox (5% ether/pentane) to yield compound **S2** as the second fraction (trace amounts). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 6.3 Hz, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.32 (p, J = 3.6, 3.0 Hz, 2H), 7.20 (dd, J = 4.2, 2.1 Hz, 3H), 6.44 (t, J = 6.4 Hz, 1H), 1.01 (d, J = 1.3 Hz, 12H), 0.86 (d, J = 1.2 Hz, 9H), -0.01 (d, J = 1.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 140.3, 132.4, 126.0, 112.1, 82.6, 26.9, 24.9, 24.5, 18.9, -2.1. (2 carbon-boron signals are not observed) ^{11}B NMR (192 MHz, $CDCl_3$) δ 40.52, 31.70. FTIR (thin film) ν cm^{-1} = 2975, 2973, 2957, 2858, 1599. HRMS (DART) calcd for $C_{22}H_{36}B_2NO_2Si$ ($[M+H]^+$) 396.2659, found 396.27078.

1.5.3 Kinetic Experiments

General Experimental Procedure for rate measurements by ^{1}H NMR

In a glovebox, a J-Young tube was charged with *N*-TBS, *B*-Mes 1,2-azaborine (25.0 mg, 80.3 μmol), 2,6-ditert-butylpyridine (40.1 mg, 241 μmol, 52.1 μL), BBr_3 in varied concentrations (0.50 M, 0.75 M, 1.13 M) and internal standard 1,1,2,2-tetrachloroethane (13.5 mg, 80.3 μmol, 8.42 μL) all in $C_2D_2Cl_4$. A ^{1}H NMR spectrum was collected every minute and disappearance of starting material was determined by the internal standard method.

1.5.4 NMR Spectra


SKB-2-BMes-COSY
SKB-2-BMes-COSY
Bpin
N
TBS
B
Mes
3a
f2 (ppm)
f1 (ppm)

SKB-2-067-1H

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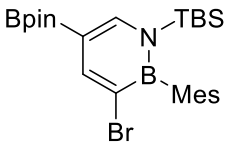
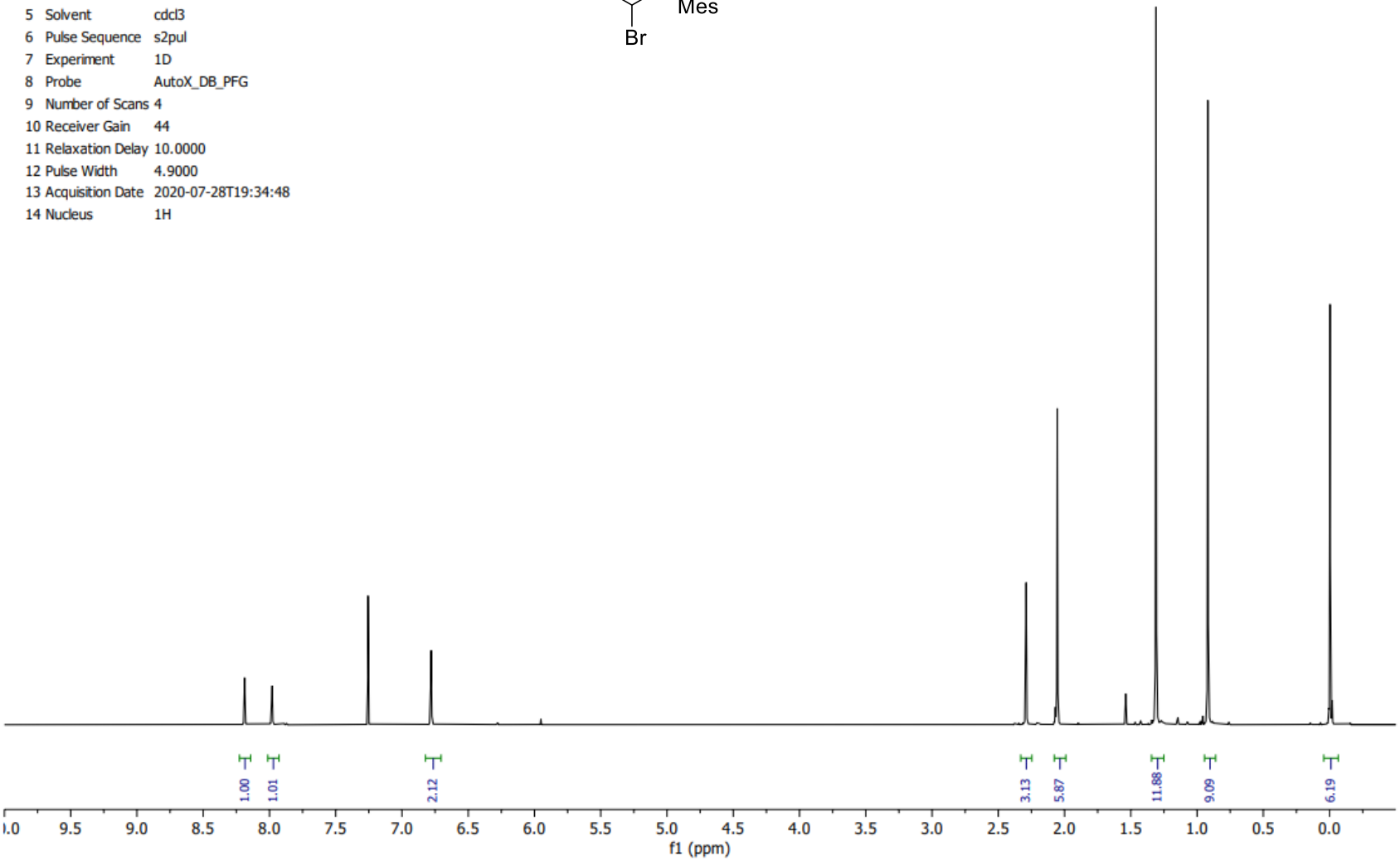
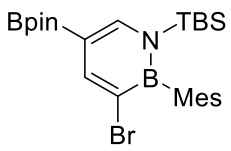
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	4
10	Receiver Gain	44
11	Relaxation Delay	10.0000
12	Pulse Width	4.9000
13	Acquisition Date	2020-07-28T19:34:48
14	Nucleus	1H





SKB-2-067-11B
SKB-2-067-11B



40.13
30.60
-3.63

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4	Instrument	vnmrs
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6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	1000
10	Receiver Gain	30
11	Relaxation Delay	0.0100
12	Pulse Width	5.9500
13	Acquisition Date	2020-07-30T13:59:48
14	Nucleus	11B

SKB-2-067-13C

STANDARD PHOSPHORUS PARAMETERS	Value
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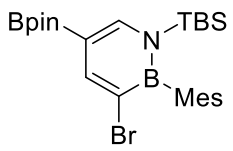
3 Origin	Varian
4 Instrument	vnmrs
5 Solvent	cdcl3
6 Pulse Sequence	s2pul
7 Experiment	1D
8 Probe	AutoX_DB_PFG
9 Number of Scans	19736
10 Receiver Gain	60
11 Relaxation Delay	1.0000
12 Pulse Width	4.8750
13 Acquisition Date	2020-07-28T19:51:08
14 Nucleus	13C



SKB-2-083-1H-F2

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4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	8
10	Receiver Gain	24
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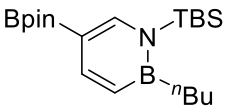
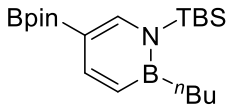
12	Pulse Width	4.3500
13	Acquisition Date	2020-08-17T20:57:45
14	Nucleus	1H



SKB-2-083-11B-F2
STANDARD PROTON PARAMETERS



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4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	286
10	Receiver Gain	30
11	Relaxation Delay	0.0100
12	Pulse Width	6.7750
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14	Nucleus	11B

SKB-2-083-13C

SKB-2-083-13C		Value
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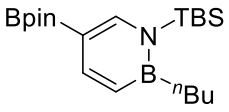
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	509
10	Receiver Gain	30
11	Relaxation Delay	1.0000
12	Pulse Width	4.8000
13	Acquisition Date	2020-08-19T14:05:43
14	Nucleus	13C



SKB-2-095-1H-F2

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4	Instrument	vnmrs
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6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	8
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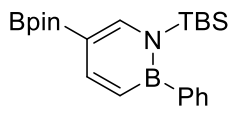
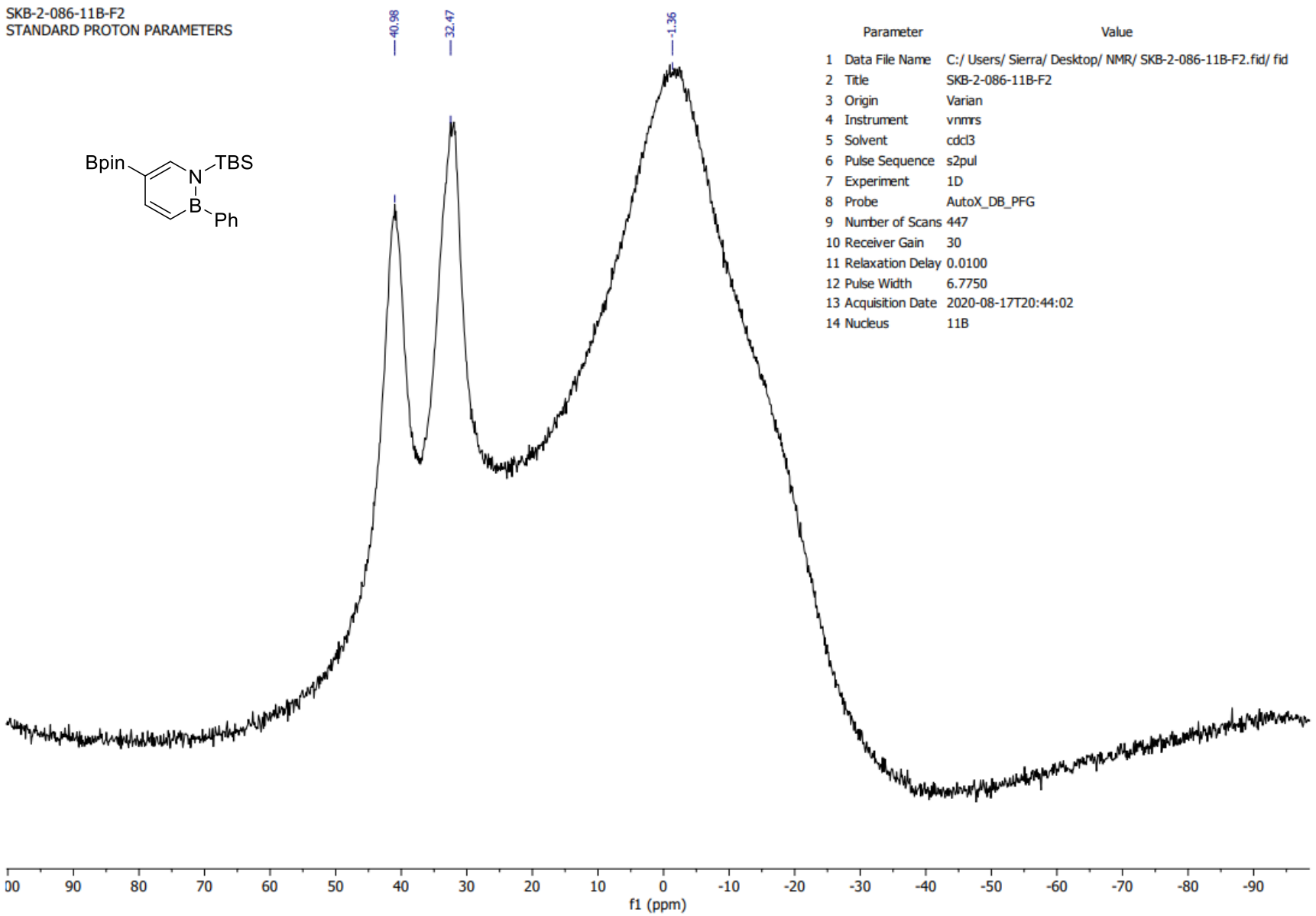
14	Nucleus	1H




SKB-2-086-11B-F2
STANDARD PROTON PARAMETERS
40.98
32.47
-1.36
Bpin
N
TBS
B
Ph
Parameter
Value
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2 Title SKB-2-086-11B-F2
3 Origin Varian
4 Instrument vnmrs
5 Solvent cdcl3
6 Pulse Sequence s2pul
7 Experiment 1D
8 Probe AutoX_DB_PFG
9 Number of Scans 447
10 Receiver Gain 30
11 Relaxation Delay 0.0100
12 Pulse Width 6.7750
13 Acquisition Date 2020-08-17T20:44:02
14 Nucleus 11B
00 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

SKB-2-C3_C5-Bpin-13C

	Parameter	Value
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3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	1030
10	Receiver Gain	30
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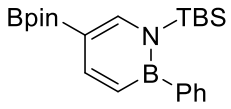
12	Pulse Width	4.8750
13	Acquisition Date	2020-09-03T11:21:42
14	Nucleus	13C



SKB-2-087-1H-F3

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4	Instrument	vnmrs
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6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	16
10	Receiver Gain	32
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12	Pulse Width	4.3500
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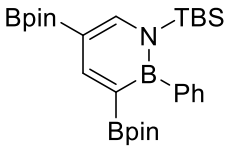
14	Nucleus	1H



SKB-2-087-11B-F3

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3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cd2cl2
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	400
10	Receiver Gain	30
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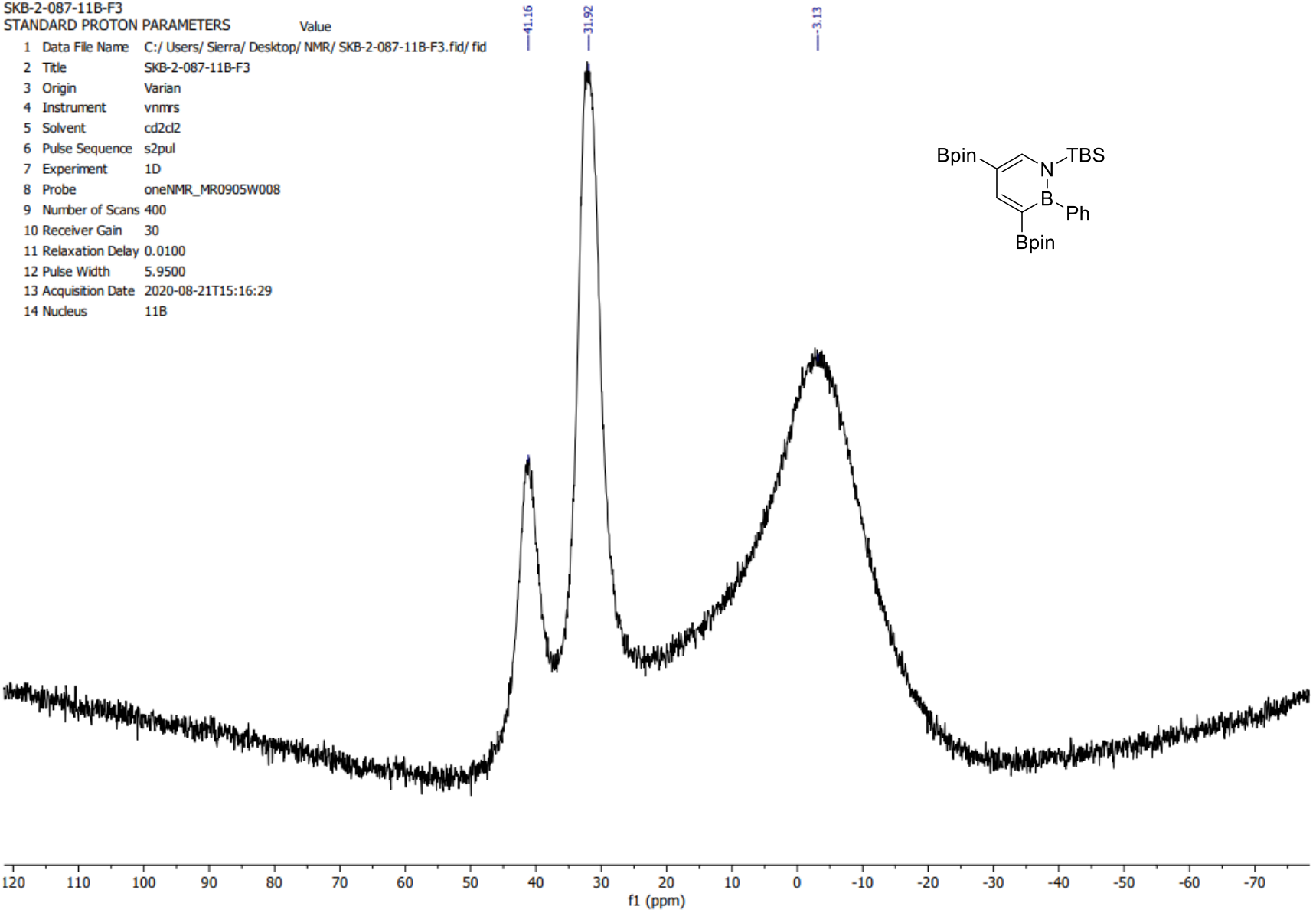
13	Acquisition Date	2020-08-21T15:16:29
14	Nucleus	11B



SKB-2-087-13C-F3

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3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cd2cl2
6	Pulse Sequence	s2pul
7	Experiment	1D
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9	Number of Scans	6948
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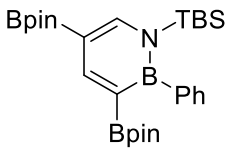
14	Nucleus	13C



SKB-2-089-1H-4h-2

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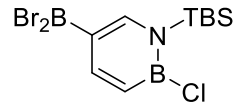
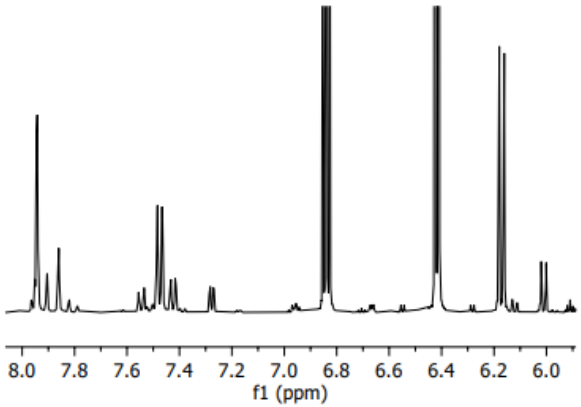
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cd2cl2
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	600_DB_AutoX_PFG_MR0902W004
9	Number of Scans	8
10	Receiver Gain	16
11	Relaxation Delay	10.0000
12	Pulse Width	5.7000
13	Acquisition Date	2020-08-23T15:32:26
14	Nucleus	1H





SKB-2-Cross-Coup-Aliquot

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4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	8
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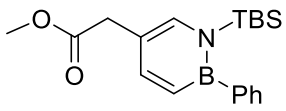
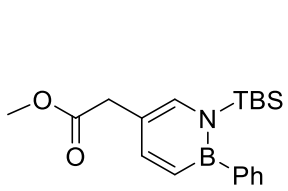
14	Nucleus	1H



SKB-2-Cross-Coup-Aliquot-11B



38.44

3.71

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4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	512
10	Receiver Gain	30
11	Relaxation Delay	0.0100
12	Pulse Width	5.9500
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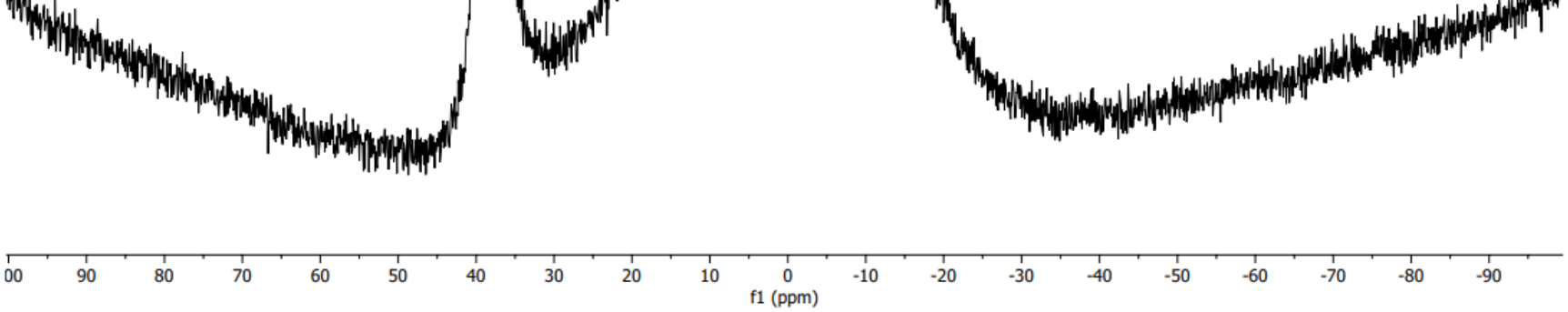
14	Nucleus	11B



SKB-2-Cross-Coup-Aliquot-13C

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3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	oneNMR_MR0905W008
9	Number of Scans	2084
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12	Pulse Width	4.8000
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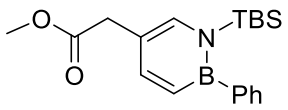
14	Nucleus	13C



SKB-2-NH-BPh-1H

SKB-2-NH-BPh-1H		Value
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4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	600_DB_AutoX_PFG_MR0902W004
9	Number of Scans	16
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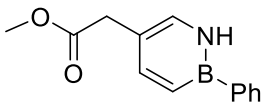
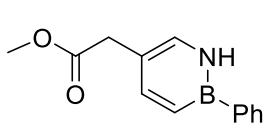
14	Nucleus	1H



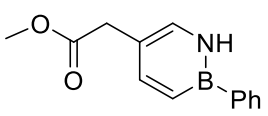
SKB-2-099-11B-F2
STANDARD PROTON PARAMETERS



	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ SKB-2-099-11B-F2.fid/ fid
2	Title	SKB-2-099-11B-F2
3	Origin	Varian
4	Instrument	inova
5	Solvent	cd2cl2
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	bb
9	Number of Scans	357
10	Receiver Gain	58
11	Relaxation Delay	0.0100
12	Pulse Width	16.2000
13	Acquisition Date	2020-08-29T19:34:03
14	Nucleus	11B

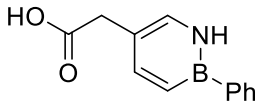
SKB-2-099-13C-F2

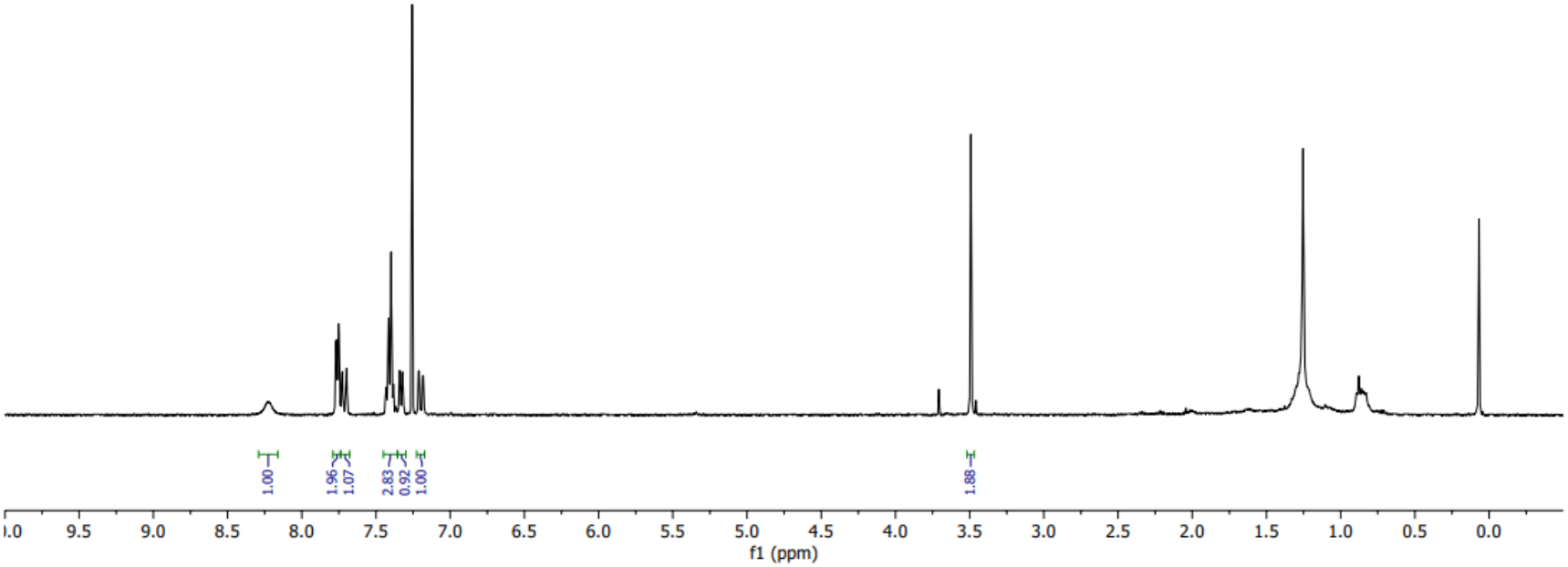
	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ Carbons/ SKB-2-099-13C-F2.fid/ fid
2	Title	SKB-2-099-13C-F2
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	1036
10	Receiver Gain	30
11	Relaxation Delay	1.0000
12	Pulse Width	4.8750
13	Acquisition Date	2020-08-31T09:51:03
14	Nucleus	13C



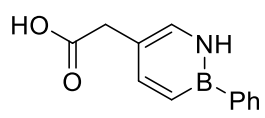
SKB-2-100-1H-60C-4h

	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ SKB-2-100-1H-60C-4h.fid/ fid
2	Title	SKB-2-100-1H-60C-4h
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	8
10	Receiver Gain	52
11	Relaxation Delay	1.0000
12	Pulse Width	4.9000
13	Acquisition Date	2020-09-02T18:38:26
14	Nucleus	1H





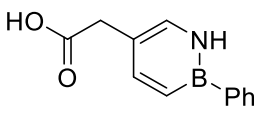
SKB-2-100-60C-4h-11B



	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ SKB-2-100-60C-4h-11B.fid/ fid
2	Title	SKB-2-100-60C-4h-11B
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	600_DB_AutoX_PFG_MR0902W004
9	Number of Scans	2000
10	Receiver Gain	30
11	Relaxation Delay	0.0100
12	Pulse Width	6.7750
13	Acquisition Date	2020-09-03T15:02:22
14	Nucleus	11B

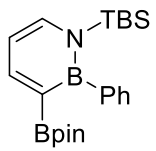
SKB-2-100-13C

	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ Carbons/ SKB-2-100-13C.fid/ fid
2	Title	SKB-2-100-13C
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	10000
10	Receiver Gain	30
11	Relaxation Delay	1.0000
12	Pulse Width	4.8750
13	Acquisition Date	2020-09-03T05:21:03
14	Nucleus	13C



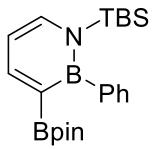
SKB-2-C3-Bpin-1H
SKB-2-C3-Bpin-1H

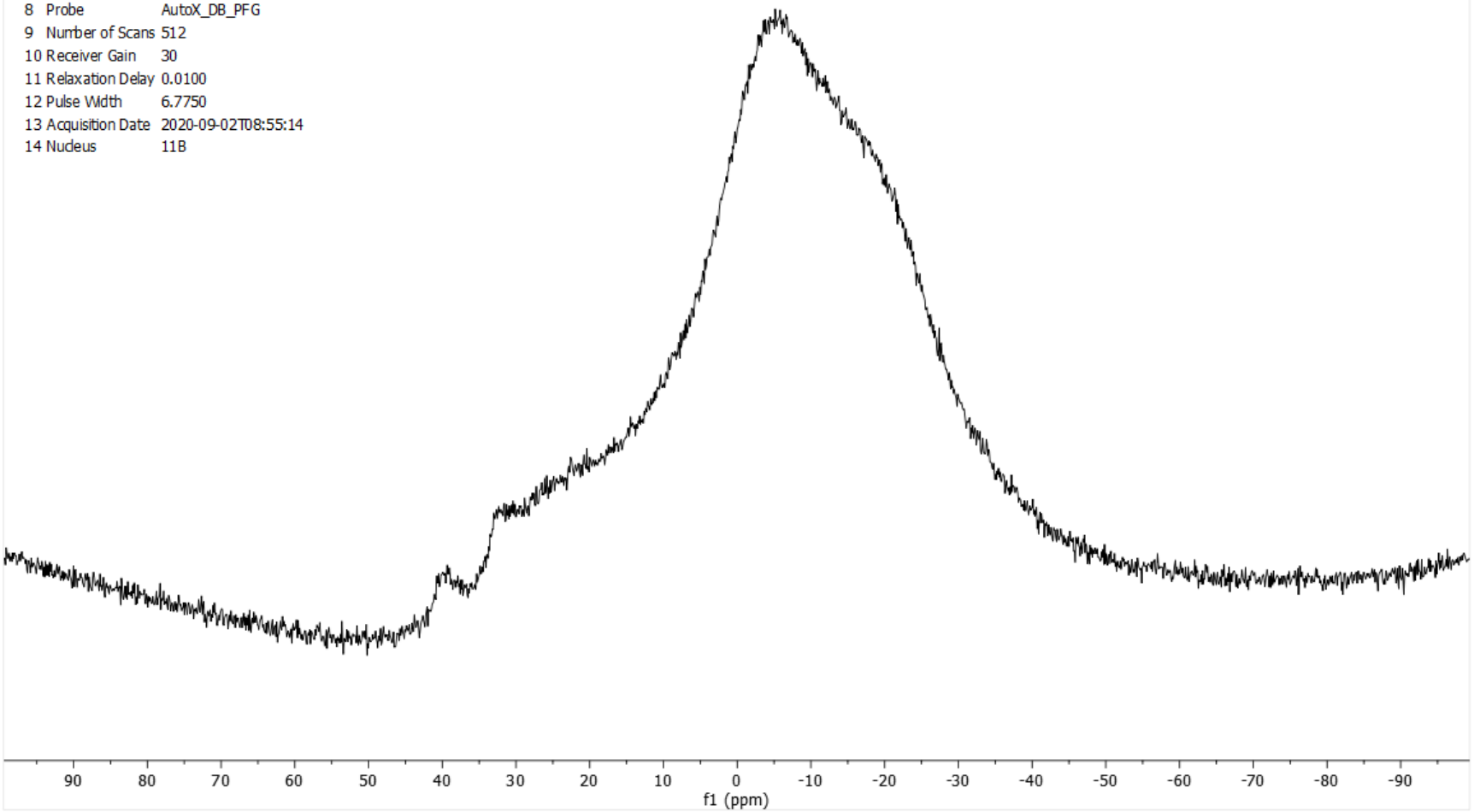
	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ C3 Bpin/ SKB-2-C3-Bpin-1H.fid/ fid
2	Title	SKB-2-C3-Bpin-1H
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdd3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	8
10	Receiver Gain	44
11	Relaxation Delay	1.0000
12	Pulse Width	4.9000
13	Acquisition Date	2020-09-02T08:43:56
14	Nucleus	1H



SKB-2-C3-Bpin-11B

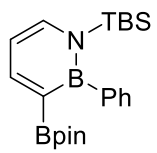
	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ C3 Bpin/ SKB-2-C3-Bpin-11B.fid/ fid
2	Title	SKB-2-C3-Bpin-11B
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	512
10	Receiver Gain	30
11	Relaxation Delay	0.0100
12	Pulse Width	6.7750
13	Acquisition Date	2020-09-02T08:55:14
14	Nucleus	11B



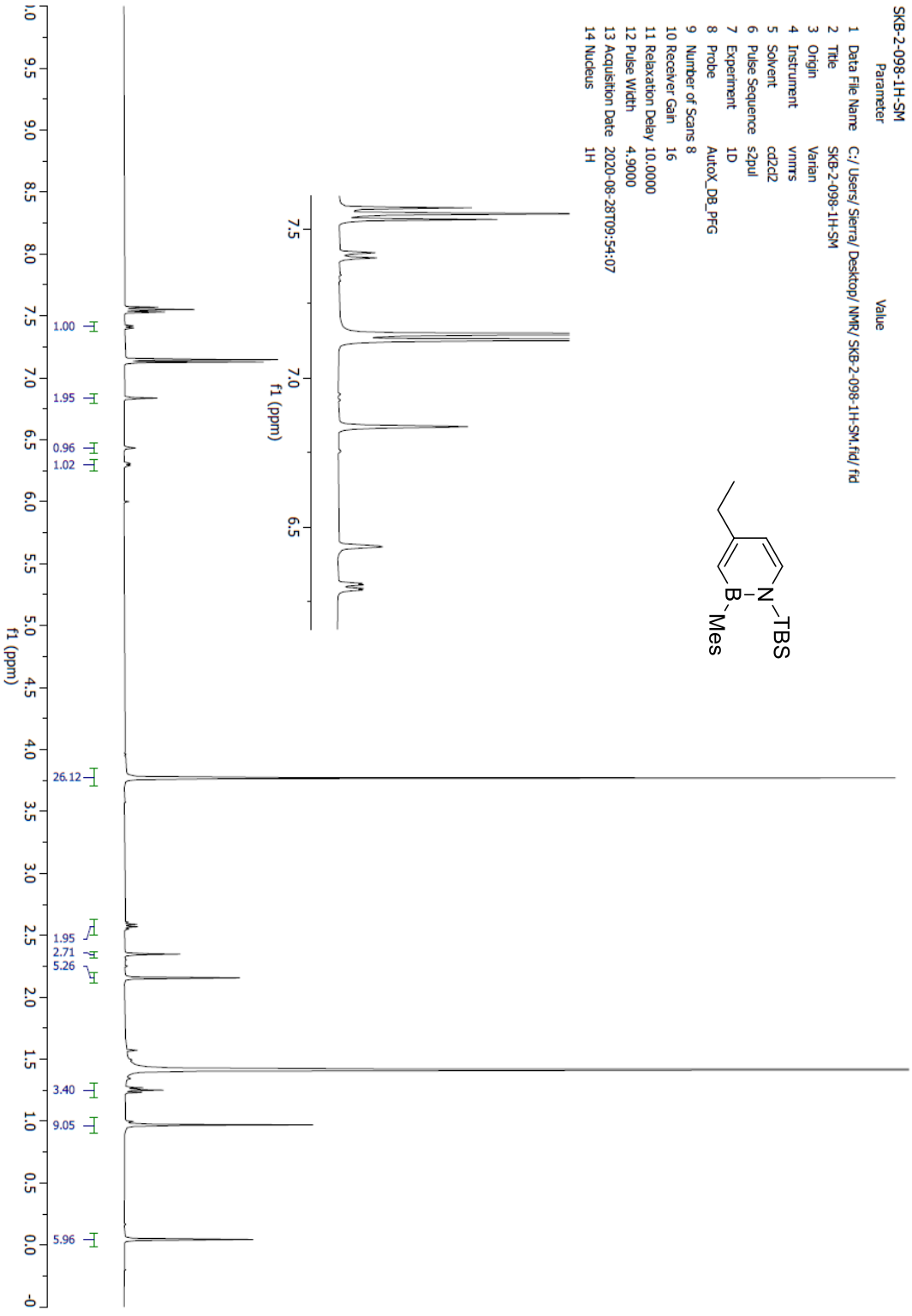


SKB-2-C3-Bpin-13C

	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ C3 Bpin/ SKB-2-C3-Bpin-13C.fid/ fid
2	Title	SKB-2-C3-Bpin-13C
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cdcl3
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	AutoX_DB_PFG
9	Number of Scans	1212
10	Receiver Gain	30
11	Relaxation Delay	1.0000
12	Pulse Width	4.8750
13	Acquisition Date	2020-09-03T12:02:21
14	Nucleus	13C

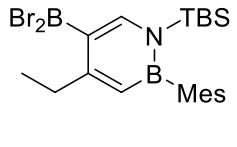


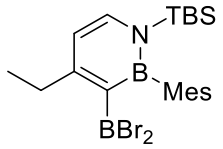
1.5.4.1 Analysis of C4 Ethyl Product

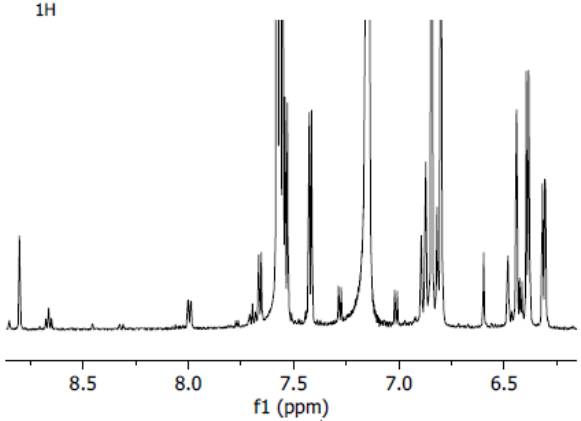


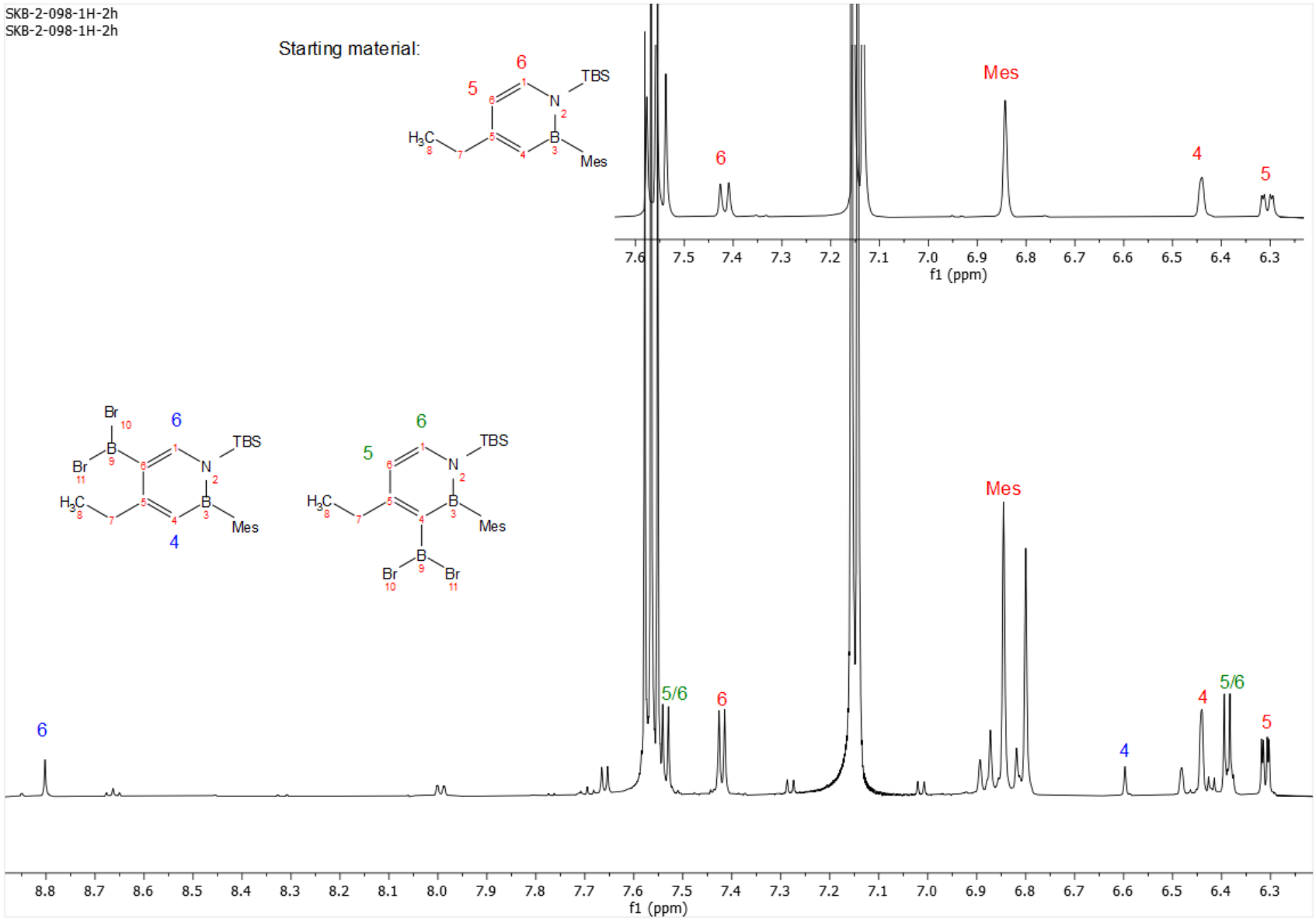
SKB-2-098-1H-2h
SKB-2-098-1H-2h

	Parameter	Value
1	Data File Name	C:/ Users/ Sierra/ Desktop/ NMR/ SKB-2-098-1H-2h.fid/ fid
2	Title	SKB-2-098-1H-2h
3	Origin	Varian
4	Instrument	vnmrs
5	Solvent	cd2cl2
6	Pulse Sequence	s2pul
7	Experiment	1D
8	Probe	600_DB_AutoX_PFG_MR0902W004
9	Number of Scans	8
10	Receiver Gain	26
11	Relaxation Delay	10.0000
12	Pulse Width	5.7000
13	Acquisition Date	2020-08-28T15:12:49
14	Nucleus	1H








SKB-2-098-1H-2h
SKB-2-098-1H-2h
Starting material:
TBS
Mes
6
5
4
Mes
f1 (ppm)
5/6
f1 (ppm)